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**3M**

March 19, 2002

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Document Processing Center (7407)
ATTN: Section 8(e) Coordinator
Office of Pollution, Prevention and Toxics
US Environmental Protection Agency
401 M Street, SW
Washington, D.C. 20460

Re: TSCA 8(e) Supplemental Notice for Sulfonate-based and Carboxylic-based
Fluorochemicals – Docket Numbers 8EHQ-1180-373; 8EHQ-1180-374; 8EHQ-0381-
0394; 8EHQ-0598-373

Dear Docket Coordinator:

With this letter, 3M is providing final reports and other supplemental information
related to previous TSCA Section 8(e) notifications. All of the enclosed items are
already in EPA's possession and available in TSCA Docket AR-226. We believe,
however, that placing these items in the 8(e) docket may allow for more convenient
access to information directly related to previous 8(e) notifications by 3M.

The reports enclosed are as follows:

1. Final Report, Identification of Fluorochemicals in Human Sera. I. American
   Red Cross Adult Blood Donors, February 25, 2002.

2. Final Report, Identification of Fluorochemicals in Human Sera. II. Elderly
   Participants of the Adult Changes in Thought Study, Seattle, Washington,
   February 25, 2002.

3. Final Report, Identification of Fluorochemicals in Human Sera. III. Pediatric
   Participants in a Group A Streptococci Clinical Trial Investigation, March 15,
   2002.

4. Interim Report #2, Determination of Serum Half-Lives of Several
   Fluorochemicals, January 11, 2002.

**EPA-OTS**

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5. Final Report, A Longitudinal Analysis of Serum Perfluorooctanesulfonate (PFOS) and Perfluorooctanoate (PFOA) in Relation to Clinical Chemistry, Thyroid Hormone, Hematology and Urinalysis Results from Male and Female Employee Participants of the 2000 Antwerp and Decatur Fluorochemical Medical Surveillance Program, October 11, 2001.

6. Final Report, A Longitudinal Analysis of Serum Perfluorooctanesulfonate (PFOS) and Perfluorooctanoate (PFOA) Levels in Relation to Lipid and Hepatic Clinical Chemistry Test Results from Male Employee Participants of the 1994/95, 1997 and 2000 Fluorochemical Medical Surveillance Program, October 11, 2001.

In addition, 3M contracted with Dr. David Gaylor of Sciences International, Inc. to calculate benchmark doses for low-dose cancer risk assessment based on the results from the cancer bioassays in rats with N-EtFOSE and PFOS. These two-year bioassay reports were submitted on February 8, 2002. Dr.Gaylor's reports provide values for the lower 95th percent confidence limit of the benchmark dose ($BMDL_{10}$) in terms of dietary concentration of N-EtFOSE or PFOS, respective to the test compound used in the study, and serum PFOS concentration, as measured at 14-weeks of dosing.

7. Benchmark Doses for Tumor in Sprague Dawley Rats fed N-Ethyl Perfluorooctanesulfonamido Ethanol (N-EtFOSE), January 31, 2002.

8. Benchmark Doses for Liver Tumors in Sprague Dawley Rats fed Perfluorooctane Sulfonic Acid Potassium Salt (PFOS), January 24, 2002.

Please contact Dr. John Butenhoff., 651-733-1962, or Dr. Geary Olsen, 651-737-8569, for further information on these studies.

Regards,

Larry R. Zobel, MD MPH
Staff Vice President & Medical Director

cc:  J.L. Butenhoff – 220-2E-02
G.W. Olsen – 220-3W-05

# FINAL REPORT
## Epidemiology
## Medical Department
## 3M Company
## St. Paul, MN 55144

Date: February 25, 2002

Title: Identification of Fluorochemicals in Human Sera. I. American Red Cross Adult Blood Donors

Study
Start Date: September 29, 2000

Protocol Number EPI-0013

Principal Investigator: Geary W. Olsen, D.V.M., Ph.D.[1]

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Study Sponsor: Corporate Occupational Medicine, Medical Department, 3M Company, 220-3W-05, St. Paul, MN 55144

1. Medical Department, 3M Company, St. Paul, MN 55144

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# ABSTRACT

Through cooperation with six American Red Cross blood banks, 645 serum samples
from adult donors (ages 20-69, equally represented of both sexes) were obtained for
fluorochemical analyses. Blood bank locations were Los Angeles (CA), Portland (OR),
Minneapolis-St. Paul (MN), Charlotte (NC), Hagerstown (MD) and Boston (MA).
Samples were void of personal identifiers. Age, gender and location were the only
known demographic factors.

Sera samples were extracted and quantitatively analyzed for seven fluorochemicals
using high-pressure liquid chromatography/electrospray tandem mass spectrometry and
evaluated versus an extracted curve from a human plasma matrix. The seven
fluorochemicals were perfluorooctanesulfonate (PFOS, $C_8F_{17}SO_3^-$); N-ethyl
perfluorooctanesulfonamidoacetate (PFOSAA, $C_8F_{17}SO_2N(CH_2CH_3)CH_2COO^-$); N-
methyl perfluorooctanesulfonamidoacetate (M570, $C_8F_{17}SO_2N(CH_3)CH_2COO^-$);
perfluorooctanesulfonamidoacetate (M556, $C_8F_{17}SO_2N(CH)CH_2COO-$);
perfluorooctanesulfonylamide (PFOSA, $C_8F_{17}SO_2NH_2$); perfluorooctanoate (PFOA,
$C_7F_{13}COO^-$); and perfluorohexanesulfonate (PFHS, $C_6F_{13}SO_3^-$).

Overall, the geometric mean measured concentration of PFOS was 34.9 ppb (95% CI
33.3-36.5). The measured PFOS concentration ranged from less than the lower limit of
quantitation (LLOQ) of 4.1 ppb to 1656.0 ppb. The geometric mean for PFOS was
significantly higher among males (37.8 ppb; 95% CI 35.5-40.3) than females (31.3 ppb;
95% CI 30.0-34.3). No significant difference was observed with age. Charlotte (NC)
had the highest geometric mean serum PFOS concentration (51.5 ppb) and Boston (MA)
the lowest (29.5 ppb). Bootstrap analyses were used to calculate a 95% tolerance limit for

PFOS of 88.5 ppb with an upper 95% confidence limit of 100.0 ppb. Additional geometric mean and tolerance limit data are reported for PFOA, PFHS, PFOSAA and M570. The geometric mean and 95% tolerance limits of these fluorochemicals were, on average, an order of magnitude (or more) lower than PFOS. PFOS and PFOA were highly correlated ($r = .63$). PFOS had lower correlations with PFOSAA ($r = .42$), PFHS ($r = .38$) and M570 ($r = .20$). The number of samples with measured PFOSA and M556 concentrations below the LLOQ prohibited meaningful statistical analyses for these compounds.

The findings from this analysis of serum PFOS concentrations are consistent with those previously reported. The human data, to date, suggests the approximate average serum concentration in non-occupational adult populations may be 30 to 40 ppb with 95% of a population's serum PFOS concentrations below 100 ppb. Since serum PFOS concentrations likely reflect cumulative human exposure, this information will be useful for risk characterization.

## INTRODUCTION

In May, 2000 the 3M Company (3M) announced that it would voluntarily cease manufacturing perfluorooctanesulfonyl- (POSF, $C_8F_{17}SO_2F$) related materials after the compound, perfluorooctanesulfonate (PFOS, $C_8F_{17}SO_3^-$), was found to be pervasive and persistent in human populations, wildlife, marine mammals and piscivorous birds (3M Company 2000; Hansen et al 2001; Giesy and Kannan 2001; Kannan et al 2001a; 2001b). POSF, produced by an electrochemical fluorination process, is used as the basic building block to create unique chemistries through the sulfonyl fluoride moiety using conventional hydrocarbon reactions. For example, POSF can be reacted with methyl or ethyl amines to produce either N-ethyl or N-methyl perfluorooctanesulfonamide. At this stage, these intermediates can be used to make amides, oxazolidinones, silanes, carboxylates and alkoxylates as commercial products. Also, these intermediates can be subsequently reacted with ethylene carbonate to form either N-ethyl or N-methyl perfluorooctanesulfonamidoethanol which can be used to make adipates, phosphate esters, fatty acid esters, urethane co-polymers and acrylates as commercialized products. Depending upon the specific functional derivatization or the degree of polymerization, such POSF-based products may degrade or metabolize, to an undetermined degree, to PFOS, a stable and persistent end-product that has the potential to bioaccumulate. While not a major commercial product, PFOS itself has been used in some products, including fire fighting foams.

The mechanisms and pathways leading to the presence of PFOS in human blood are not well characterized but likely involve environmental exposure to PFOS or its precursor molecules and residual levels of PFOS or PFOS precursors in industrial and commercial

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products. PFOS has been detected at low parts per billion (ppb) concentrations in the general population (Hansen et al 2001; 3M Company 2000) although the scope of these investigations has been limited. Using high pressure liquid chromatography/electrospray tandem mass spectrometry, Hansen et al (2001) detected an average PFOS concentration of 28.4 ppb (SD 13.6; range 6.7-81.5) in 65 commercial individual human sera samples. An analysis of pooled blood samples (n = 3 to 6 pooled samples per location with 5 to 100 donors per pooled sample) from 18 blood banks in the United States resulted in a mean measured PFOS serum concentration of 30 ppb with a range from 9 to 56 ppb (3M Company, 2000). Serum PFOS concentrations among production employees working in POSF-related processes were approximately 2 parts per million (ppm) depending on work activity (range 0.1 to 12 ppm) (Olsen et al 1999).

The purpose of this study was to better characterize the distribution of seven fluorochemicals, including PFOS and some of its precursors in an adult population by analyzing sera samples obtained from donors at six American Red Cross blood banks. An assessment of the serum fluorochemical distribution was performed in relation to three demographic attributes (age, gender and location) of the anonymous blood donors.

## METHODS

### Fluorochemicals

The seven analytes detected and quantified in this study were: PFOS; N-ethyl perfluorooctanesulfonamidoacetate (PFOSAA, $C_8F_{17}SO_2N(CH_2CH_3)CH_2COO^-$); N-methyl perfluorooctanesulfonamidoacetate (M570, $C_8F_{17}SO_2N(CH_3)CH_2COO^-$); perfluorooctanesulfonamido acetate (M556, $C_8F_{17}SO_2N(CH)CH_2COO^-$);

perfluorooctanesulfonylamide (PFOSA, $C_8F_{17}SO_2NH_2$); perfluorooctanoate (PFOA, $C_7F_{13}COO^-$); and perfluorohexanesulfonate (PFHS, $C_6F_{13}SO_3^-$).

PFOSAA is an oxidation product of N-ethyl perfluorooctanesulfonamidoethanol (N-EtFOSE) and is a residual in N-EtFOSE-related chemistry which was primarily used in paper and packaging protectant applications. M570 is an oxidation product of N-methyl perfluorooctanesulfonamidoethanol (N-MeFOSE) and is a residual of N-MeFOSE-related chemistry which was used primarily in surface treatment applications (e.g., carpets, textiles). Therefore, PFOSAA and M570 can be considered markers of consumer-related exposure. Both PFOSAA and M570 can metabolize to M556 and PFOSA which, in turn can subsequently metabolize to PFOS. Unlike PFOSAA and M570, M556, PFOSA and PFOS are not specific to any one consumer application. Unlike the other analytes, PFOA and PFHS are not precursors, metabolites or residuals of PFOS. PFOA can be a residual by-product of the production of the POSF-related manufacturing electrochemical fluorination process and was produced by 3M to be an emulsifier in a variety of industrial applications (e.g., ammonium salt) (Olsen et al 2000). PFOA can also be an oxidation product or metabolite of the widely used telomer-based fluorochemicals manufactured by other companies. PFHS, the sulfonate form of perfluorohexane sulfonyl fluoride (PHSF), is a residual by-product of POSF-related production. 3M produced the PHSF as a building block compound incorporated in fire fighting foams and specific post-market carpet treatment applications.

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## Sample Collection

Through cooperation with six American Red Cross blood banks, 645 serum samples from adult donors (ages 20 - 69, equally represented of both sexes) were obtained for analysis. [Note: This final report supercedes the June 25, 2001 3M interim report which indicated 652 samples. Seven samples were not included in the final report because the subjects were determined to be ineligible by age ($\geq$ 70). Additional separate 3M sponsored studies were designed to examine the distribution of serum samples among elderly adults and children.] The six American Red Cross blood banks represented donors from the following areas: Los Angeles, CA; Portland, OR; Minneapolis-St. Paul, MN; Charlotte, NC; Hagerstown, MD and Boston, MA. Samples were void of personal identifiers. The only known demographic factors were age, gender and location. Each blood bank was requested to provide approximately 10 samples per 10 year age intervals (20-29, 30-39, 40-49, 50-59 and 60-69) for each sex.

## Fluorochemical Analysis

Northwest Bioanalytical (Salt Lake City, Utah) analyzed the serum for the target fluorochemicals using techniques similar to those described by Hansen et al (2001). Details of the specific analytical procedures are presented elsewhere (NWB 2002). Briefly, the analytical method consisted of a liquid:liquid extraction procedure followed by evaporation and reconstitution of the extract residue with 20 mM ammonium acetate in water:20 mM ammonium acetate in methanol (30:70, v/v). The samples were analyzed by high pressure liquid chromatography/tandem mass spectrometry. Quantitation of the target analytes in serum samples was performed by comparing the

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chromatographic peak areas for each compound to those generated in a series of extracted

calibration standards prepared from control Chinese plasma. The samples were injected

in a systematic order. Evaluation of quality control samples injected during each

analytical run indicated that the reported quantitative results may have varied, on average,

up to 26 percent using human plasma calibration curves for all analytes except PFOSA

which may have varied on average up to 43 percent.

Also presented in this report is a calculated total organic fluorine (TOF) index.

TOF was the percent of each of the seven fluorochemicals' molecular weight that was

attributed to organic fluorine [PFOS (64.7%); PFHS (61.9%); PFOA (69.0%); PFOSAA

(55.3%); PFOSA (64.7%); M570 (56.6%) and M556 (58.1%)] multiplied by the ppb

measured for each fluorochemical and then summed across all seven fluorochemicals.


Data Analysis

Measures of central tendency applicable to log normally distributed data (median,

geometric mean) were used for descriptive analyses. In those instances where a sample

was measured below the lower limit of quantitation (LLOQ), the midpoint between zero

and the LLOQ was used for calculation of the geometric mean. An assessment of this

midpoint assumption and how it affected the calculation of the geometric mean was

performed using the 10th and 90th percentile values between zero and the LLOQ for those

values <LLOQ.

In order to minimize parametric assumptions in the estimation of extreme

percentiles of the population, the bootstrap method of Efron (1993) was used to generate

confidence intervals around the empirical percentiles for serum concentrations. In this

method, a large number of replicated estimates of the percentile are generated from full-size samples of the original observations drawn with replacement. The distribution of the deviations of replicates from the original-sample estimate mimics the underlying sampling distribution for the estimate. Bias-corrected, accelerated percentiles were used to minimize residual bias. The bias correction factor is derived by comparing empirical percentiles to bootstrap percentiles and acceleration is accomplished by partial jackknifing.

Twenty-four samples were split and analyzed to provide an estimate of the reliability of the analyses conducted. The analytical laboratory was blind to the identity of these split samples. These analyses were performed concurrently with all other analyses of the study to minimize experimental error. Five split samples were analyzed from Charlotte, Los Angeles, Hagerstown and Portland and four split samples from Boston. Inadvertently, no reliability analyses were performed on the Minnesota samples.

## RESULTS

The results for the reliability analysis for PFOS, PFOA and PFHS are displayed in Figure 1. Only six split samples for PFOSAA and seven split samples for M570 had values that were above the LLOQ. None of the PFOSA and M556 split samples were above the LLOQ. Therefore, only the reliability results for PFOS, PFOA and PFHS are displayed in Figure 1. There was a strong correlation between the split samples (r = .9 for each of these three fluorochemicals. It should be noted that 13 of the split sample analyses for PFHS had the identical LLOQ (2.1 ppb). This is represented in the graph as the single point near the abscissa (0,0) on the identity (ln y = ln x) line.

Provided in Table 1 is the distribution of the donor subjects by 10 year age intervals, gender and location. Altogether there were 332 male donors and 313 female donors. As could be expected with the age stratification design used for sample collection, the study subjects' mean ages were comparable by gender: 44.6 years for males and 43.9 years for females.

The measured concentrations of PFOSA and M556 were predominantly below the LLOQ. For PFOSA, there was one subject with a value above (2.1 ppb) the LLOQ, 196 subjects <LLOQ (1.0 ppb) and 448 subjects <LLOQ (1.4 ppb). The different LLOQ values were determined on different analytical runs. For M556, twelve subjects were above the LLOQ. Their M556 values ranged from 3.6 to 12.9 ppb. There were 145 subjects with M556 values <LLOQ (2.5 ppb) and 488 subjects with M556 values <LLOQ (3.2 ppb). Because of the few subjects whose serum concentrations exceeded the LLOQ, statistical analyses are not presented for PFOSA and M556. Although PFOSA and M556 are not presented in the subsequent analyses, they were included in the calculation of the TOF index. For those measured concentrations of PFOSA and M556 < LLOQ, the midpoint between zero and the LLOQ was used in the calculation of the TOF index.

The frequency distributions of the five remaining fluorochemicals, PFOS, PFOA, PFHS, PFOSAA and M570, are displayed in Figure 2. Although the graphs are suggestive of log normal distributions, only the PFOS distribution met such criteria based on the Shapiro-Wilk test. This lack of log normality is due to the greater percentage of subjects with values <LLOQ for PFOA, PFHS, PFOSAA and M570.

The range, interquartile range, number of samples < LLOQ. raw cumulative 90th percentile. median, geometric mean and 95% confidence interval of the geometric mean

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for PFOS, PFOA, PFHS, PFOSAA and M570 are provided in Table 2 for all subjects, males only and females only. Overall, the geometric mean levels of PFOS was 34.9 ppb (95% CI 33.3-36.5). The range of PFOS values was < LLOQ (4.3 ppb) to 1656.0 ppb. Male subjects had significantly (p < .05) higher geometric means for PFOS than female subjects [male geometric mean = 37.8 ppb (95% CI 35.5-40.3) vs female geometric mean = 32.1 ppb (95% CI 30.0-34.3)]. Males also had significantly higher serum levels of PFOA and PFHS compared to females although the mean levels for both sexes were approximately one order of magnitude lower than that of PFOS. It should be noted that the overall geometric mean for the calculated TOF index was 31.7 ppb (95% CI 30.4 - 33.0) (data not shown). The calculated TOF index ranged from 5.7 ppb to 1083.2 ppb.

Provided in Figure 3 is a graphical distribution (natural log scale) of the five fluorochemicals by 10 year age intervals stratified by gender. The box covers the interquartile range of the natural log distribution. The circle within the box is the mean. The whiskers extend to the last observation within 1.5 times the interquartile range. The dots with lines through them represent observations outside the 1.5 times interquartile range. As shown in Figure 3, age was not an important predictor of adult serum fluorochemical concentrations. In those instances where there were many outliers (e.g.. M570 concentrations in males aged 40-49 and 60-69), this was the result of a large percentage of values <LLOQ that were within the 1.5 x interquartile range.

As discussed previously in the Methods, the geometric mean data were calculated under the assumption that for individual serum fluorochemical values <LLOQ the midpoint between zero and the LLOQ was assigned. For PFOS, only one subject had a value <LLOQ; thus this assumption did not affect its calculation of the geometric mean.

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However, considerably more subjects had LLOQs for PFOA, PFHS, PFOSAA and M570 (see Table 2). If these values were assumed to be 10% or 90% of this range between zero and the LLOQ the respective range of the geometric means (95% confidence interval in parenthesis) became: PFOA 4.0 ppb (3.7-4.1) to 4.8 ppb (4.6-5.0); PFHS 0.9 ppb (08-1.0) to 2.5 ppb (2.4-2.6); PFOSAA 0.8 ppb (0.7-0.9) to 2.8 ppb (2.7-3.0) and M570 0.5 ppb (0.5-0.6) to 1.9 ppb (1.8-2.0). These geometric mean values were not substantially different than those calculated using the midpoint between zero and the <LLOQ as presented in Table 2. Consequently, the midpoint between zero and the LLOQ was used for the analyses.

Presented in Table 3 are the range, interquartile range and medians for the six locations combined across age and gender for the five fluorochemicals. A graphical presentation of these data (natural log scale) is presented in Figure 4. Interpretation of the graphs is comparable to those discussed above for Figure 3. Provided in Table 4 are the results from a bootstrap analysis which calculated mean serum fluorochemical values for each of the six locations adjusted for 10 year age intervals, gender and their interaction terms. The highest mean value for PFOS was Charlotte (39.0 ppb) with the lowest being Boston (29.0 ppb). Los Angeles, Minneapolis-St. Paul and Hagerstown had comparable mean PFOS levels of approximately 35.0 ppb with Portland slightly lower (32.8 ppb). The range of means for the other fluorochemical analytes was narrow and thus difficult to distinguish any substantial differences by location. Because PFOS is the primary contributor to the calculated TOF index, the bootstrap analysis findings for TOF mirrored those of PFOS.

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Scatter plots (log scale) between the five fluorochemicals are displayed in Figure 5. PFOS and PFOA were highly correlated ($r = .63$). PFOS had a lower correlation with PFOSAA ($r = .42$) and lower yet with M570 ($r = .20$). The correlation between PFOSAA and M570 was weak ($r = .12$). The remaining scatter plots display the correlation between PFOS and PFHS ($r = 0.38$) and PFOA and PFHS ($r = 0.32$). Both PFOSAA and M570, adjusted for age, gender and their interaction, were significant predictors of PFOS in a multivariable model albeit PFOSAA was the stronger of the two independent variables (Table 5). Nevertheless, approximately eighty percent of the variation of PFOS was left unexplained. Age and gender were not significant predictors in models that examined the significant association between PFOS and PFOA (Table 6) or PFHS (Table 7). None of the models in Tables 5 through 7 had lack of fit F ratios that were statistically significant ($p < .05$).

Presented in Table 8 are the results from bootstrap analyses conducted to provide mean concentrations of several tolerance limits. The tolerance limits represent the limit of each fluorochemical within which the stated proportion of the population is expected to be found. Presented are the mean values of the five serum fluorochemicals and TOF for the 90th, 95th and 99th percent tolerance limits along with the upper limit (bound) from the 95% confidence interval. For example, the mean of the 95% tolerance limit for PFOS was 88.5 ppb with an upper 95% confidence limit of 100.0 ppb. At the lowest tolerance limit analyzed (90%), the mean for PFOS was 70.7 ppb with an upper 95% confidence limit of 74.3 ppb. At the highest tolerance limit analyzed (99%), the mean was 157.3 ppb with an upper 95% confidence limit of 207.0 ppb. For other fluorochemicals analyzed, the mean of the 95% tolerance limit for PFOA was 12.1 ppb with an upper 95%

confidence limit of 13.6 ppb. For PFHS, the mean of the 95% tolerance limit was 9.5 ppb with an upper 95% confidence limit of 10.8 ppb. The mean of the 95% tolerance limit for PFOSAA was 7.6 ppb with an upper 95% confidence limit of 8.5 ppb. For M570, the mean was 5.0 ppb for a 95% tolerance limit with an upper 95% confidence limit of 5.4 ppb. Finally, for the calculated index of TOF, the mean was 75.1 ppb for the 95% tolerance limit with an upper 95% confidence limit of 80.9 ppb.

## DISCUSSION

The findings from this analysis of serum PFOS concentrations in 645 adult donors are consistent with previous human data. Previous measurements of human serum samples obtained in the United States showed mean PFOS concentrations of 30 ppb in 18 pooled blood banks, 44 ppb from a pooled commercial sample of 500 donors, 33 ppb from a different pooled commercial sample of 200 donors and 28 ppb in 65 commercial individual human sera samples (3M Company 2000; Hansen et al 2001). These findings were also comparable to a limited number of European samples which found mean serum PFOS concentrations at 17 ppb in 5 pooled samples from a Belgium blood bank, 53 ppb in 6 pooled samples from the Netherlands and 37 ppb from 6 pooled blood samples from Germany and 39 individual Swedes whose serum PFOS ranged between <LLOQ 32 ppb to 85 ppb (3M Company, 2000). The mean calculated TOF index of 31.7 ppb in the present study was also consistent with the low ppb total organic fluorine measurements of general population samples that have been reported since the 1960's (Taves 1968; Taves et al 1976; Singer and Ophaug 1979; Belisle 1981).

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Unique to the present study was its large individual sample size which facilitated the characterization of the serum fluorochemical distribution. This included the calculation of tolerance limits and their upper bounds. The highest serum PFOS measurement (confirmed by re-assay of the sample) was 1656.0 ppb. Because donor samples were anonymous, it is not possible to determine anything about this individual besides gender (male), age (67 years) and location (Portland). This PFOS sample approximated the average serum PFOS levels observed for POSF-related production workers (Olsen et al 1999). The next highest donor level for PFOS was considerably lower at 329 ppb (also a male, age 62 from the Portland area) and the subsequent next eight highest serum PFOS values (range 139 ppb to 226 ppb) were measured in four females and four males representing Charlotte (n = 4), Hagerstown (n = 2), Los Angeles (n = 1) and Minneapolis-St. Paul (n = 1). Also distinctive to this effort was the study's capability to examine potential associations between PFOS and age (no association) and gender (males slightly higher than females).

Our findings showed a strong correlation between PFOS and PFOA. Whereas PFOS has been routinely measured in human populations, wildlife, marine mammals and piscivorous birds (Giesy and Kannan 2001; Kannan et al 2001a; 2001b; Hansen et al 2001), serum PFOA concentrations, to date, have been consistently quantified (i.e., measured above the LLOQs) primarily in humans. This association is of significant interest because PFOA cannot convert directly from PFOS (or vice versa). Whether this association is due to the presence of PFOA as a by-product in POSF-related production or to other non-related environmental exposures or consumer products from other manufacturers (e.g., higher chain telomers) remains to be answered. Another

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unanswered question is whether perfluoroctanesulfonamides can metabolize in humans to PFOA. Any of these explanations coupled with the suspected long serum half-lives in humans for PFOS (8.7 years (SD = 6.1) and PFOA (4.4 years (SD = 3.5) as reported by Burris et al (2002), could explain the strong correlation between PFOS and PFOA.

PFOS was also correlated with two fluorochemicals, PFOSAA and M570, known to be analytes from exposure to consumer products involving paper/packaging and carpet/textile protectants, respectively. Overall, the data, to date, indicate that PFOS bioaccumulation in animals may be primarily through environmental sources whereas both environmental and product exposures likely contribute to serum PFOS concentrations in humans (Giesy and Kannan 2001; Kannan et al 2001a; 2001b).

As with any interpretation of data obtained from a study population, questions arise regarding the representativeness and ability to generalize the data collected. Clearly, American Red Cross blood donors are a self-selected group from the United States population (Leibrecht et al 1976; Oswalt 1977; Burnett 1982; Allen and Butler 1993; Andaleeb and Basu 1995; Chiavette et al 2000). Motivations to donate have included altruism, desire for personal credit, low self-esteem, social pressure and test-seeking behavior. Motivations not to donate have included fear, medical excuses, apathy and inconvenience. Donors tend to have a greater trust in institutions, more interest in their personal health and higher risk-taking behavior. Demographically, white males and older individuals have historically constituted a larger percentage of the donor pool. Donors also tend to be more educated, married and have more children than nondonors. In the present study, donors were not asked whether a sample of their blood donation could be used for fluorochemical assay nor was there any linkage between the sample

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collected and personal identifiers. No information was obtained about past exposure histories to POSF-related chemistries and materials (or the other fluorochemicals that were analyzed). Therefore, we believe the selection process of donors used in this study resulted in a reasonable representation of the overall blood donor population that was providing blood at the time when these donors were sampled. We are unaware of any database that can be considered generalizable to the diverse United States general adult population without measures of random and systematic bias incorporated in the data analysis.

Given the consistency of the data analyzed, to date, we hypothesize that the average serum PFOS concentrations in non-occupational adult populations likely ranges between 30 to 40 ppb with 95% of a population's serum PFOS concentrations below 100 ppb. Understanding these serum PFOS levels in human populations will be useful for risk characterization since serum PFOS likely reflects cumulative human exposure (3M Company 2000). Currently available data (unpublished reports to U.S. EPA:Docket No. FYI-0500-01378) suggest that the serum concentrations observed in humans are substantially less than those required to cause adverse effects in laboratory animals (3M Company 2000).

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## ACKNOWLEDGEMENTS

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# REFERENCES

3M Company (2000). SIDS Initial Assessment Report Perfluorooctane Sulfonic Acid and its Salts. St. Paul:3M Company, September 20, 2000.

Allen J, Butler DD (1993). Assessing the effects of donor knowledge and perceived risk on intentions to donate blood. J Health Care Market 13:26-33.

Andaleeb SS, Basu AK (1995). Explaining blood donation: the trust factor. J Health Care Market 15:42-48.

Belisle J (1981). Organic fluorine in human serum: natural versus industrial sources. Science 212:1509-1510.

Burnett JJ (1982). Examining the profiles of the donor and nondonor through a multiple discriminant approach. Transfusion 22:136-142.

Burris JM, Lundberg JK, Olsen GW, Simpson C, Mandel JH (2002). Interim Report: Determination of serum half-lives of several fluorochemicals. St. Paul:3M Company, January 11, 2002.

Chiavetta J, Ennis M, Gula CA, Baker AD, Chambers TL (2000). Test-seeking as motivation in volunteer blood donors. Transfusion Med Rev 14:205-215.

Efron B, Tibshiarani RJ. An Introduction to the Bootstrap. In: Cox DR, Hinkley DV. Reid N, Rubin DB, Silverman BW, eds. Monographs on Statistics and Applied Probability. Vol 57 New York:Chapman H Hall.

Giesy JP, Kannan K (2001). Global distribution of perfluorooctane sulfonate in wildlife. Environ Sci Technol 35(7):1339-1342.

Hansen KJ, Clemen LA, Ellefson ME, Johnson HO (2001a). Compound-specific quantitative characterization of organic fluorochemicals in biological matrices. Environ Sci Technol 35:766-770.

Kannan K, Koistenen J, Beckmen K, Evans T, Gorzelany JF, Hansen KJ, Jones PD, Helle E, Nyman M, Giesy JP (2001b). Accumulation of perfluorooctane sulfonate in marine mammals. Environ Sci Technol 35(8):1593-1598.

Kannan K, Franson JC, Bowerman WW, Hansen KJ, Jones PD, Giesy JP (2001). Perfluorooctane Sulfonate in fish-eating water birds including bald eagles and albatrosses. Environ Sci Technol 35(15):3065-3070.

Leibrecht BC, Hogan JM, Luz GA, Tobias KI (1976). Donor and nondonor motivations. Transfusions 16:182-189.

Northwest Bioanalytical (NWB, 2002). Quantitative determination of PFOS and related compounds in human serum by LC/MS/MS January 9, 2002.

Olsen GW, Burris JM, Mandel JH, Zobel LR (1999). Serum perfluorooctane sulfonate and hepatic and lipid clinical chemistry tests in fluorochemical production employees. JOEM 41:799-806.

Olsen GW, Burris JM, Burlew MM, Mandel JH (2000). Plasma cholecystokinin and hepatic enzymes, cholesterol and lipoproteins in ammonium perfluorooctanoate production workers. Drug Chem Toxicol 23:603-620.

Oswalt RM (1977). A review of blood donor motivation and recruitment. Transfusion 17:123-135.

Singer L, Phaug RH (1979). Concentrations of ionic, total, and bound fluoride in plasma. Clin Chem 25:523-525.

Taves D (1968). Evidence that there are two forms of fluoride in human serum. Nature 217:1050-1051.

Taves D, Guy W, Brey W (1976). Organic fluorocarbons in human plasma: Prevalence and characterization. In: Filler R, eds. Biochemistry Involving Carbon-Fluorine Bonds. Washington DC:American Chemical Society, pp 117-134.

Table 1

Distribution of American Red Cross Blood Donor Subjects by Age, Gender and Location

| Location | Males | | | | | | Females | | | | | | Overall Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 20 - 29 | 30 - 39 | 40 - 49 | 50 - 59 | 60 - 69 | Subtotal | 20 - 29 | 30 - 39 | 40 - 49 | 50 - 59 | 60 - 69 | Subtotal | |
| Los Angeles | 14 | 11 | 15 | 13 | 10 | 63 | 16 | 12 | 12 | 12 | 10 | 62 | 125 |
| Boston | 12 | 11 | 11 | 11 | 12 | 57 | 10 | 11 | 10 | 11 | 10 | 52 | 109 |
| Minneapolis – St. Paul | 10 | 10 | 10 | 10 | 10 | 50 | 10 | 10 | 10 | 10 | 10 | 50 | 100 |
| Charlotte | 10 | 10 | 10 | 10 | 7 | 47 | 10 | 11 | 10 | 10 | 8 | 49 | 96 |
| Portland | 10 | 11 | 10 | 15 | 10 | 56 | 10 | 11 | 10 | 11 | 9 | 51 | 107 |
| Hagerstown | 10 | 10 | 10 | 10 | 19 | 59 | 10 | 10 | 10 | 10 | 9 | 49 | 108 |
| | 66 | 63 | 66 | 69 | 68 | 332 | 66 | 65 | 62 | 64 | 56 | 313 | 645 |

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Table 2

Measures of Central Tendency of Serum Fluorochemicals for American Red Cross Blood Donors (N = 645) by Gender

| | PFOS | PFOA | PFHS | PFOSAA | M570 |
|---|---|---|---|---|---|
| **All (N = 645)** | | | | | |
| Range | <LOQ (4.3) – 1656.0 | <LOQ (1.9) – 52.3 | <LOQ (1.4) – 66.3 | <LOQ (1.6) – 60.1 | <LOQ (1.0) – 16.4 |
| Q1 – Q3 | 24.7 – 48.5 | 3.4 – 6.6 | <LOQ (2.1) – 3.4 | <LOQ (2.8) – 3.4 | <LOQ (1.8) – 2.2 |
| <LOQ (Number) | <4.3 (1) | <1.9 (2) | <1.4 (72) | <1.6 (101) | <1.0 (63) |
| | | <2.1 (48) | <2.1 (235) | <2.8 (271) | <1.8 (326) |
| Cumulative 90% | 70.7 | 9.4 | 6.3 | 5.2 | 3.8 |
| Median | 35.8 | 4.7 | 1.5 | <LOQ (2.8) | <LOQ (1.8) |
| Geometric Mean | 34.9 | 4.6 | 1.9 | 2.0 | 1.3 |
| 95% C.I. Geometric Mean | 33.3 – 36.5 | 4.3 – 4.8 | 1.8 – 2.0 | 1.9 – 2.1 | 1.3 – 1.4 |
| **Males (N = 332)** | | | | | |
| Range | <LOQ (4.3) – 1656.0 | <LOQ (1.9) – 29.0 | <LOQ (1.4) – 66.3 | <LOQ (1.6) – 60.1 | <LOQ (1.0) – 16.4 |
| Q1 – Q3 | 28.3 – 49.7 | 3.6 – 7.0 | <LOQ (2.1) – 3.8 | <LOQ (2.8) – 3.3 | <LOQ (1.8) – 2.2 |
| <LOQ (Number) | | <2.1 (19) | <1.4 (30) | <1.6 (58) | <1.0 (36) |
| | | | <2.1 (104) | <2.8 (146) | <1.8 (163) |
| Cumulative 90% | 72.6 | 10.1 | 7.9 | 4.7 | 3.5 |
| Median | 37.4 | 4.9 | 2.1 | <LOQ (2.8) | <LOQ (1.8) |
| Geometric Mean | 37.8 | 4.9 | 2.2 | 1.9 | 1.3 |
| 95% C.I. Geometric Mean | 35.5 – 40.3 | 4.6 – 5.3 | 2.0 – 2.4 | 1.8 – 2.1 | 1.2 – 1.4 |

## Females (N = 313)

| | | | | | |
|---|---|---|---|---|---|
| Range | 6.0 – 226.0 | <LOQ (2.1) – 52.3 | <LOQ (1.4) – 15.3 | <LOQ (1.6) – 27.6 | <LOQ (1.0) – 10.6 |
| Q1 – Q3 | 22.0 – 45.8 | 3.1 – 6.2 | <LOQ (2.1) – 2.8 | <LOQ (2.8) – 3.6 | <LOQ (1.8) – 2.2 |
| <LOQ (Number) | | <1.9 (2) | <1.4 (42) | <1.6 (43) | <1.0 (27) |
| | | <2.1 (29) | <2.1 (131) | <2.8 (125) | <1.8 (163) |
| Cumulative 90% | 69.7 | 8.4 | 5.0 | 6.1 | 4.0 |
| Median | 31.3 | 4.4 | <LOQ (2.1) | <LOQ (2.8) | <LOQ 1.8 |
| Geometric Mean | 32.1 | 4.2 | 1.6 | 2.1 | 1.3 |
| 95% C.I. Geometric Mean | 30.0 – 34.3 | 3.9 – 4.5 | 1.5 – 1.8 | 2.0 – 2.3 | 1.2 – 1.4 |

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Table 3

Measures of Central Tendency of Fluorochemicals by the Six American Red Cross Blood Bank Locations

| | PFOS | PFOA | PFHS | PFOSAA | M570 |
|---|---|---|---|---|---|
| **Los Angeles** | | | | | |
| Range | 6.6 – 205.0 | <LOQ (2.1) – 34.1 | <LOQ (2.1) – 12.4 | <LOQ (2.8) – 27.6 | <LOQ (1.8) – 16.4 |
| Q1 – Q3 | 29.5 – 53.7 | 2.9 – 6.6 | <LOQ (2.1) – 3.0 | <LOQ (2.8) – 4.2 | <LOQ (1.8) – 2.2 |
| Cumulative 90% | 70.1 | 9.2 | 5.8 | 6.1 | 4.8 |
| Median | 42.2 | 4.6 | <LOQ (2.1) | 3.1 | <LOQ (1.8) |
| Geometric Mean | 40.4 | 4.1 | 1.9 | 2.6 | 1.4 |
| 95% C.I. Geometric Mean | 37.0 – 44.0 | 3.6 – 4.7 | 1.7 – 2.1 | 2.4 – 3.0 | 1.2 – 1.6 |
| **Boston** | | | | | |
| Range | <LOQ (4.3) – 87.2 | 1.5 – 13.9 | <LOQ (1.4) – 12.6 | <LOQ (1.6) – 6.7 | <LOQ (1.8) – 13.0 |
| Q1 – Q3 | 20.8 – 39.1 | 4.1 – 7.3 | <LOQ (2.1) – 3.0 | <LOQ (1.6) – 2.9 | <LOQ (1.8) – 2.4 |
| Cumulative 90% | 48.7 | 9.7 | 5.4 | 4.1 | 3.5 |
| Median | 29.5 | 5.5 | 2.1 | <LOQ (2.8) | 1.8 |
| Geometric Mean | 28.0 | 5.4 | 1.9 | 1.6 | 1.4 |
| 95% C.I. Geometric Mean | 25.4 – 31.0 | 5.0 – 5.8 | 1.6 – 2.2 | 1.4 – 1.8 | 1.2 – 1.6 |

## Mpls. – St. Paul

| | | | | | |
|---|---|---|---|---|---|
| Range | 7.7 – 207.0 | <LOQ (1.9) – 20.0 | <LOQ (1.4) – 15.2 | <LOQ (1.6) – 12.9 | <LOQ (1.0) – 10.6 |
| Q1 – Q3 | 23.9 – 43.3 | 3.2 – 5.7 | <LOQ (1.4) – 2.8 | <LOQ (1.6) – 2.6 | <LOQ (1.0) – 2.3 |
| Cumulative 90% | 71.7 | 9.9 | 5.7 | 4.9 | 4.0 |
| Median | 31.7 | 4.4 | 1.4 | 1.4 | 1.3 |
| Geometric Mean | 33.1 | 4.5 | 1.5 | 1.6 | 1.2 |
| 95% C.I. Geometric Mean | 29.8 – 36.7 | 4.0 – 5.0 | 1.3 – 1.8 | 1.4 – 1.8 | 1.0 – 1.4 |

## Charlotte

| | | | | | |
|---|---|---|---|---|---|
| Range | 19.3 – 166.0 | <LOQ (2.1) – 29.0 | <LOQ (1.4) – 22.4 | <LOQ (1.6) – 60.1 | <LOQ (1.0) – 10.8 |
| Q1 – Q3 | 36.3 – 70.9 | 4.5 – 8.6 | 1.5 – 4.8 | <LOQ (2.8) – 4.2 | <LOQ (1.8) – 2.8 |
| Cumulative 90% | 105.3 | 13.3 | 10.9 | 8.6 | 4.7 |
| Median | 48.9 | 6.3 | 2.8 | 1.8 | 1.2 |
| Geometric Mean | 51.5 | 6.3 | 2.8 | 2.4 | 1.5 |
| 95% C.I. Geometric Mean | 46.8-56.8 | 5.6-7.1 | 2.4-3.4 | 1.9-2.9 | 1.3-1.8 |

**Portland**

| | | | | | |
|---|---|---|---|---|---|
| Range | 6.0 – 1656.0 | <LOQ (2.1) – 16.7 | <LOQ (2.1) – 11.8 | <LOQ 2.8) – 36.9 | <LOQ (1.8) – 6.9 |
| Q1 – Q3 | 17.2 – 37.7 | 2.8 – 4.7 | <LOQ (2.1) – 2.5 | <LOQ (2.8) – 3.8 | <LOQ (1.8) – 2.9 |
| Cumulative 90% | 49.4 | 6.8 | 5.5 | 7.4 | 2.9 |
| Median | 26.0 | 3.8 | <LOQ (2.1) | <LOQ (2.8) | <LOQ (1.8) |
| Geometric Mean | 27.0 | 3.6 | 1.6 | 2.5 | 1.3 |
| 95% C.I. Geometric Mean | 23.5 – 31.1 | 3.2 – 4.0 | 1.4 – 1.8 | 2.2 – 2.9 | 1.2 – 1.5 |

**Hagerstown**

| | | | | | |
|---|---|---|---|---|---|
| Range | 7.6 – 226.0 | <LOQ (2.1) – 52.3 | <LOQ (2.1) – 66.3 | <LOQ (2.8) – 21.2 | <LOQ (1.8) – 7.9 |
| Q1 – Q3 | 24.4 – 48.1 | 3.2 – 5.9 | <LOQ (2.1) – 3.8 | <LOQ (2.8) – 1.4 | <LOQ (1.8) – 1.9 |
| Cumulative 90% | 69.8 | 7.6 | 7.3 | 3.4 | 3.1 |
| Median | 35.7 | 4.7 | 2.1 | <LOQ (2.8) | <LOQ (1.8) |
| Geometric Mean | 35.3 | 4.2 | 2.1 | 1.7 | 1.2 |
| 95% C.I. Geometric Mean | 31.8 – 39.2 | 3.8 – 4.8 | 1.7 – 2.4 | 1.5 – 1.9 | 1.1 – 1.4 |

Table 4
Mean and 95% Confidence Intervals Calculated from Bootstrap Analyses
For the Six Locations, Adjusted for Age, Gender and Their Interaction Term

| | PFOS | | PFOA | | PFHS | | PFOSAA | | M570 | | TOF | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | 95% CI | Mean | 95% CI | Mean | 95% CI | Mean | 95% CI | Mean | 95% CI | Mean | 95% CI |
| Los Angeles | 35.0 | 33.4 – 36.5 | 4.6 | 4.4 – 4.8 | 1.9 | 1.8 – 2.0 | 2.0 | 1.9 – 2.2 | 1.3 | 1.3 – 1.4 | 30.2 | 29.0 – 31.3 |
| Boston | 29.0 | 26.0 – 30.3 | 5.3 | 4.6 – 5.6 | 1.9 | 1.7 – 2.3 | 1.6 | 1.4 – 1.8 | 1.3 | 1.2 – 1.5 | 26.4 | 23.9 – 29.2 |
| Minneapolis – St. Paul | 34.8 | 31.9 – 36.3 | 4.5 | 4.1 – 4.7 | 1.8 | 1.6 – 2.0 | 1.8 | 1.7 – 2.1 | 1.3 | 1.1 – 1.4 | 29.7 | 27.4 – 32.1 |
| Charlotte | 39.0 | 36.2 – 40.7 | 5.0 | 4.6 – 5.1 | 2.2 | 2.0 – 2.4 | 2.1 | 1.9 – 2.4 | 1.4 | 1.3 – 1.5 | 33.4 | 31.3 – 35.7 |
| Portland | 32.8 | 30.5 – 34.2 | 4.3 | 4.0 – 4.4 | 1.8 | 1.7 – 2.0 | 2.1 | 2.0 – 2.3 | 1.3 | 1.2 – 1.4 | 28.5 | 26.7 – 30.4 |
| Hagerstown | 34.9 | 32.8 – 36.5 | 4.5 | 4.2 – 4.6 | 1.9 | 1.8 – 2.1 | 1.9 | 1.8 – 2.1 | 1.3 | 1.2 – 1.4 | 30.1 | 28.4 – 31.9 |

Table 5
Multivariable Regression Model of PFOS* by PFOSAA*, M570*,
Age, Gender and Age x Gender Interaction

|  | Coefficient | SE | t ratio | p value |
|---|---|---|---|---|
| Intercept | 3.3 | 0.07 | 46.3 | < .0001 |
| PFOSAA* | 0.3 | 0.03 | 11.7 | < .0001 |
| M570* | 0.1 | 0.03 | 4.1 | < .0001 |
| Age | - 0.001 | 0.001 | -0.8 | .40 |
| Gender | - 0.2 | 0.07 | -2.4 | .02 |
| Age x Gender | 0.001 | 0.001 | 0.9 | .35 |

N = 645

*Natural log

Adjusted $r^2$ = 0.22

Gender: females =1; males = 0

t ratio = coefficient/SE (standard error)

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Table 6
Multivariable Regression Model of PFOS[*] by PFOA[*]
Age, Gender and Age x Gender Interaction

|  | Coefficient | SE | t ratio | p value |
|---|---|---|---|---|
| Intercept | 2.7 | 0.07 | 36.4 | < .0001 |
| PFOA[*] | 0.6 | 0.03 | 20.3 | < .0001 |
| Age | - 0.001 | 0.001 | -1.0 | .29 |
| Gender | 0.02 | 0.06 | 0.4 | .72 |
| Age x Gender | -0.001 | 0.001 | -1.0 | .31 |

N = 645

[*]Natural log

Adjusted $r^2 = 0.40$

Gender: females = 1; males = 0

t ratio = coefficient/SE (standard error)

000031

Table 7
Multivariable Regression Model of PFOS* by PFHS*
Age, Gender and Age x Gender Interaction

|  | Coefficient | SE | t ratio | p value |
|---|---|---|---|---|
| Intercept | 3.4 | 0.07 | 45.5 | < .0001 |
| PFHS* | 0.3 | 0.03 | 9.9 | < .0001 |
| Age | -0.0003 | 0.002 | -0.2 | .84 |
| Gender | -0.06 | 0.07 | -0.8 | .43 |
| Age x Gender | 0.0002 | 0.002 | 0.2 | .87 |

N = 645

*Natural log

Adjusted $r^2 = 0.15$

Gender: females = 1; males = 0

t ratio = coefficient/SE

000032

Table 8. Tolerance Limits and Their Associated Mean and Upper 95th
Percent Confidence Limits for Serum Fluorochemicals and Calculated
Total Organic Fluorine Index

|  | Tolerance Limit | Mean | Upper 95th Percent Confidence Limit |
|---|---|---|---|
| PFOS | 90% | 70.7 | 74.3 |
|  | 95% | 88.5 | 100.0 |
|  | 99% | 157.3 | 207.0 |
| PFOA | 90% | 9.4 | 10.1 |
|  | 95% | 12.1 | 13.6 |
|  | 99% | 19.8 | 25.8 |
| PFHS | 90% | 6.3 | 7.0 |
|  | 95% | 9.5 | 10.8 |
|  | 99% | 17.0 | 22.4 |
| PFOSAA | 90% | 5.3 | 5.9 |
|  | 95% | 7.6 | 8.5 |
|  | 99% | 19.4 | 27.6 |
| M570 | 90% | 3.7 | 4.0 |
|  | 95% | 5.0 | 5.4 |
|  | 99% | 8.1 | 10.3 |
| TOF | 90% | 59.9 | 63.1 |
|  | 95% | 75.1 | 80.9 |
|  | 99% | 137.3 | 187.5 |

Figure 1. Analysis of Split Samples for Reliability Assessment for PFOS, PFOA and PFHS
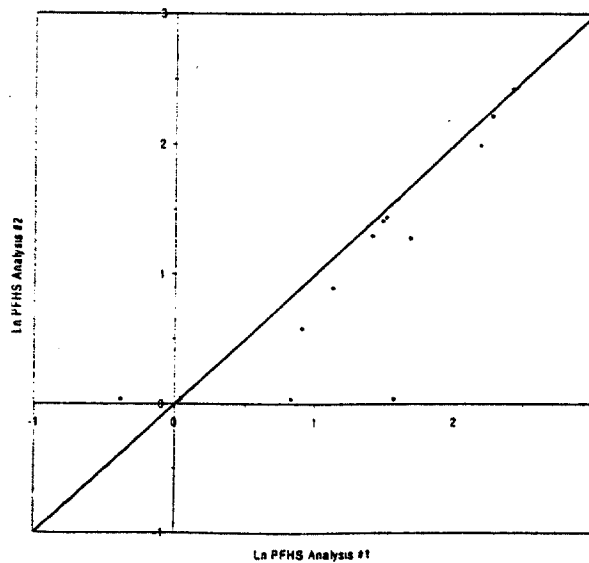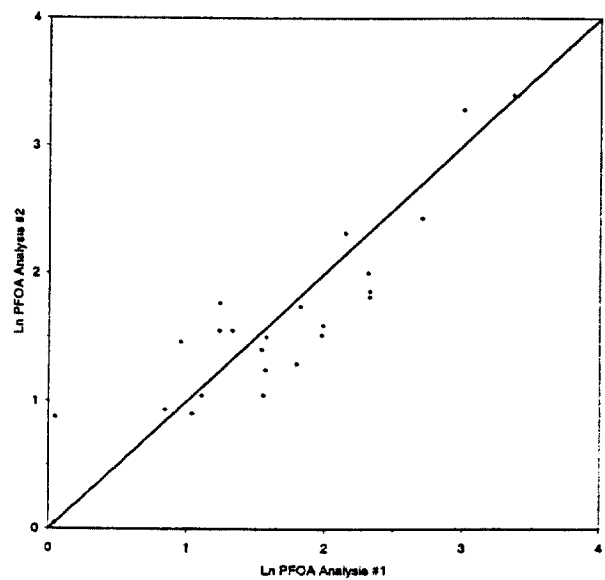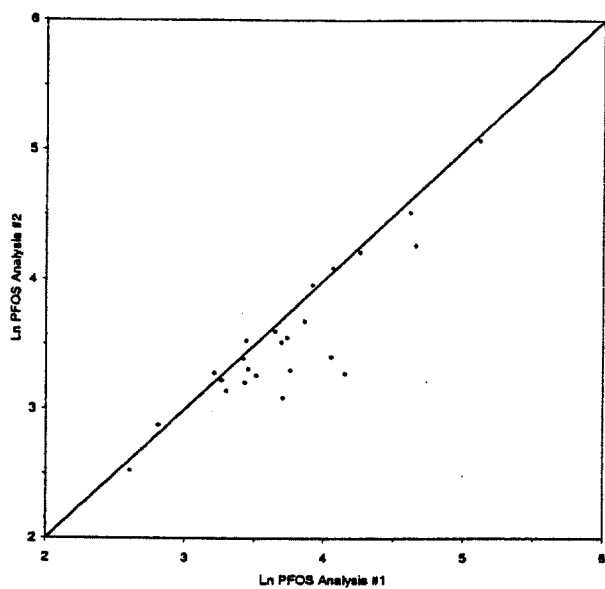
Figure 2. Adult Study Population Distribuion of Measured Fluorochemical Concentrations
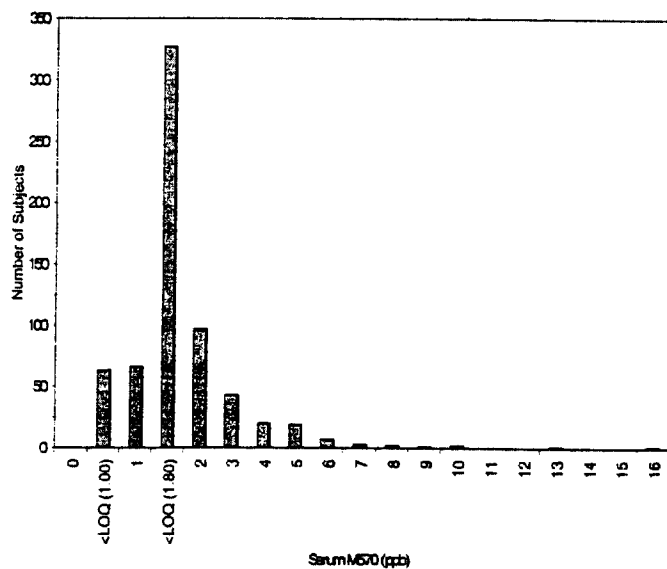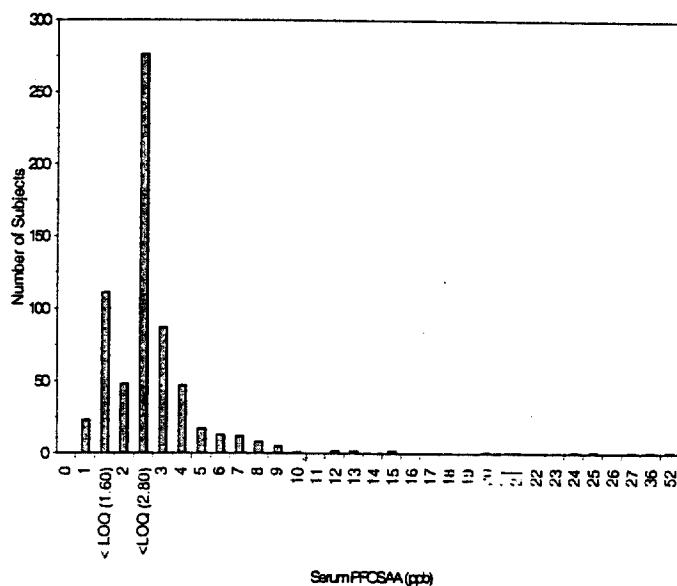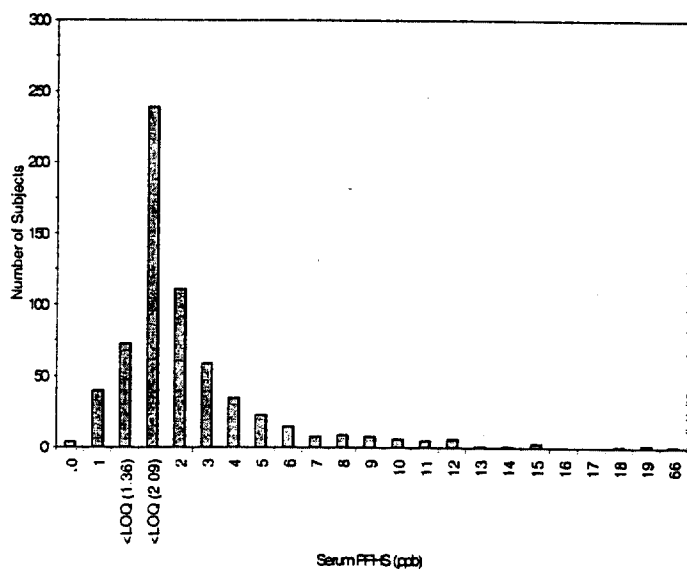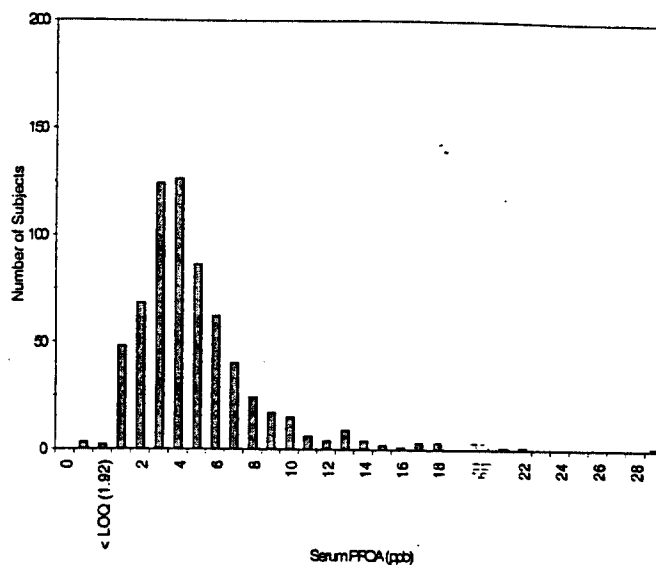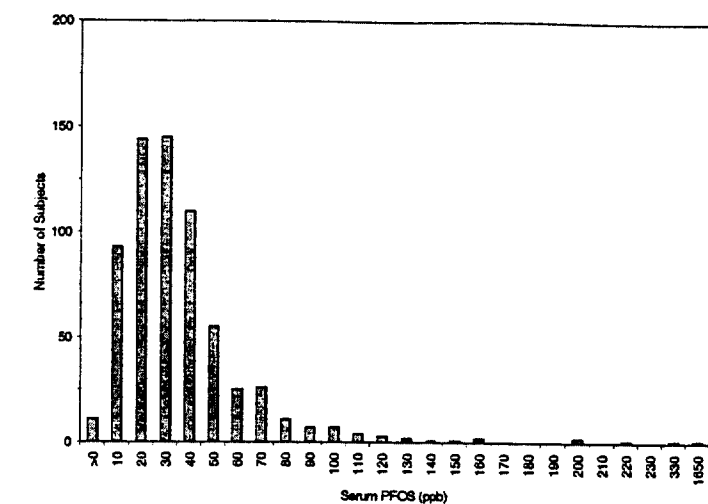
33

Figure 3. Box and Whisker Plots of Serum Fluorochemical Concentrations by Age and Gender
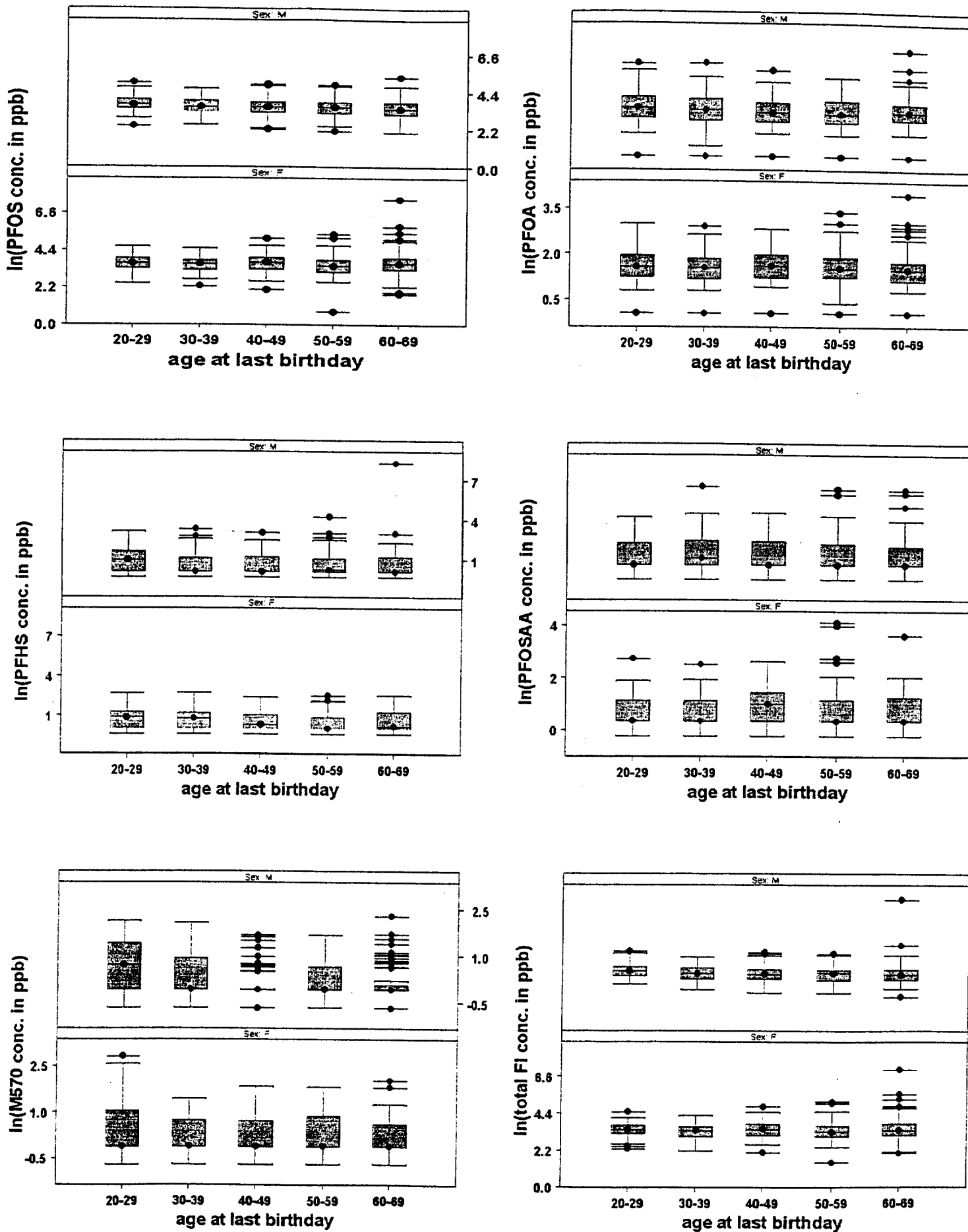
Figure 4. Box and Whisker Plots of Serum Fluorochemical Concentrations by Age and ___ ___
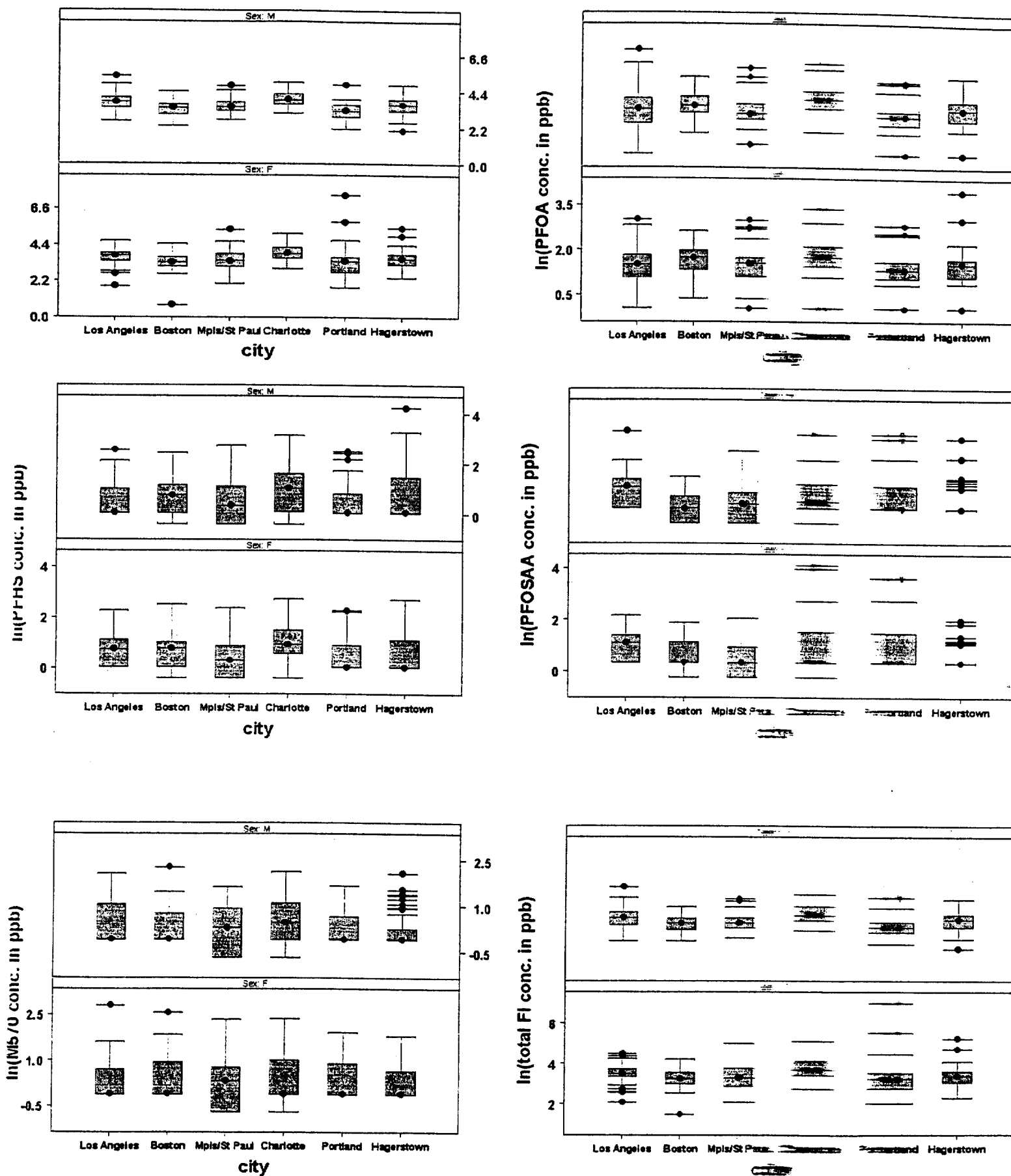
Figure 5. Scatter Plots (log scale) of Fluorochemical Associations

# FINAL REPORT
Epidemiology
Medical Department
3M Company
St. Paul, MN 55144

Date: February 25, 2002

Title: Identification of Fluorochemicals in Human Sera. II. Elderly Participants of the Adult Changes in Thought Study, Seattle, Washington

Study
Start Date:     September 29, 2000

Protocol Number EPI-0016

Principal Investigator:          Geary W. Olsen, D.V.M., Ph.D.[1]

3M Co-investigators:             Jean M. Burris, M.P.H., R.N.[1]
                                 James K. Lundberg, Ph.D.[2]
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Study Sponsor:                   Corporate Occupational Medicine, Medical Department, 3M Company, 220-3W-05, St. Paul, MN 55144


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## ABSTRACT

A total of 238 serum samples from elderly volunteers from a large prospective longitudinal study designed to examine cognitive function among male and female subjects, ages 65-96, in the Seattle (WA) area were obtained for fluorochemical analyses. Samples were void of personal identifiers. The only known demographic factors were: age, gender and the number of years residence in Seattle.

Sera samples were extracted and quantitatively analyzed for seven fluorochemicals using high-pressure liquid chromatography/electrospray tandem mass spectrometry. The seven fluorochemicals detected were perfluorooctanesulfonate (PFOS, $C_8F_{17}SO_3^-$); N-ethyl perfluorooctanesulfonamidoacetate (PFOSAA, $C_8F_{17}SO_2N(CH_2CH_3)CH_2COO^-$); N-methyl perfluorooctanesulfonamidoacetate (M570, $C_8F_{17}SO_2N(CH_3)CH_2COO^-$); perfluorooctanesulfonamidoacetate (M556, $C_8F_{17}SO_2N(CH)CH_2COO^-$); perfluorooctanesulfonylamide (PFOSA, $C_8F_{17}SO_2NH_2$); perfluorooctanoate (PFOA, $C_7F_{13}COO^-$); and perfluorohexanesulfonate (PFHS, $C_6F_{13}SO_3^-$).

Overall, the geometric mean measured concentration of PFOS was 31.0 ppb (95% CI 28.8-33.4). The measured PFOS concentration ranged from less than the lower limit of quantitation (LLOQ) of 3.4 ppb to 175.0 ppb. There was no significant difference in the PFOS geometric means by sex or years residence in Seattle. Age was negatively associated with PFOS. Bootstrap analyses were used to calculate a 95% tolerance limit for PFOS of 84.1 ppb with an upper 95% confidence limit of 104.0 ppb. Additional geometric mean and tolerance limit data are reported for PFOA, PFHS, PFOSAA and M570. The geometric means and tolerance limits for these fluorochemicals were, on average, an order of magnitude (or more) lower than PFOS. There was a strong

correlation between PFOS and PFOA (r = .75). PFOS had lower correlations with PFOSAA and PFHS (r = .42) and lower yet with M570 (r = .29). The number of samples with measured concentrations of PFOSA and M556 below the LLOQ prohibited meaningful statistical analysis of these compounds.

The findings from this analysis of serum PFOS concentrations are consistent with serum PFOS levels of 645 American Red Cross blood donors, ages 20-69. These and other data suggest the average serum concentration in the non-occupational adult population data approximates 30 to 40 ppb with 95% of the population's serum PFOS concentrations below 100 ppb. Since serum PFOS concentrations likely reflect cumulative human exposure, this information will be useful for risk characterization.

## INTRODUCTION

In May, 2000 the 3M Company (3M) announced that it would voluntarily cease manufacturing perfluorooctanesulfonyl- (POSF, $C_8F_{17}SO_2F$) related production after the compound, perfluorooctanesulfonate (PFOS, $C_8F_{17}SO_3^-$), was found to be pervasive and persistent in human populations, wildlife, marine mammals and piscivorous birds (3M Company 2000; Hansen et al 2001; Giesy and Kannan 2001; Kannan et al 2001a; 2001b). POSF, produced by an electrochemical fluorination process, is used as the basic building block to create unique chemistries through the sulfonyl fluoride moiety using conventional hydrocarbon reactions. For example, POSF can be reacted with methyl or ethyl amines to produce either N-ethyl or N-methyl perfluorooctanesulfonamide. At this stage, these intermediates can be used to make amides, oxazolidinones, silanes, carboxylates and alkoxylates as commercial products. Also, these intermediates can be subsequently reacted with ethylene carbonate to form either N-ethyl or N-methyl perfluorooctanesulfonamidoethanol which can be used to make adipates, phosphate esters, fatty acid esters, urethane co-polymers and acrylates as commercialized products. Depending upon the specific functional derivatization or the degree of polymerization, such POSF-based products may degrade or metabolize, to an undetermined degree, to PFOS, a stable and persistent end-product that has the potential to bioaccumulate. While not a major commercial product, PFOS itself has been used in some products, including fire fighting foams.

The mechanisms and pathways leading to the presence of PFOS in human blood are not well characterized but likely involve environmental exposure to PFOS or its precursor molecules and residual levels of PFOS or PFOS precursors in industrial and commercial

products. PFOS has been detected at low parts per billion (ppb) concentrations in the

general population (Hansen et al 2001; 3M Company 2000) although the scope of these

investigations has been limited. Using high pressure liquid chromatography/electrospray

tandem mass spectrometry, Hansen et al (2001) detected an average PFOS concentration

of 28.4 ppb (SD 13.6; range 6.7-81.5) in 65 commercial individual human sera samples.

An analysis of pooled blood samples (n = 3 to 6 pooled samples per location with 5 to 10

donors per pooled sample) from 18 blood banks in the United States resulted in a mean

measured PFOS serum concentration of 30 ppb with a range from 9 to 56 ppb (3M

Company, 2000). Serum PFOS concentrations among production employees working in

POSF-related processes were approximately 2 parts per million (ppm) depending on

work activity (range 0.1 to 12 ppm) (Olsen et al 1999).

The purpose of this study was to better characterize the distribution of seven

fluorochemicals, including PFOS and some of its precursors, in the human population by

using individual sera samples obtained from elderly subjects enrolled in the Adult

Changes in Thought (ACT) study (McCurry et al 1999). An assessment of the serum

fluorochemical distribution was performed in relation to three demographic attributes

(age, gender and years lived in the Seattle metropolitan area) of the study subjects.


## METHODS

### Fluorochemicals

The seven analytes detected and quantified in this study were: PFOS; N-ethyl

perfluorooctanesulfonamidoacetate (PFOSAA, $C_8F_{17}SO_2N(CH_2CH_3)CH_2COO^-$); N-

methyl perfluorooctanesulfonamidoacetate (M570, $C_8F_{17}SO_2N(CH_3)CH_2COO^-$);

perfluorooctanesulfonamido acetate (M556, $C_8F_{17}SO_2N(CH)CH_2COO^-$);

perfluorooctanesulfonylamide (PFOSA, $C_8F_{17}SO_2NH_2$); perfluorooctanoate (PFOA, $C_7F_{13}COO^-$); and perfluorohexanesulfonate (PFHS, $C_6F_{13}SO_3^-$).

PFOSAA is an oxidation product of N-ethyl perfluorooctanesulfonamidoethanol (N-EtFOSE) and is a residual in N-EtFOSE-related chemistry which was primarily used in paper and packaging protectant applications. M570 is an oxidation product of N-methyl perfluorooctanesulfonamidoethanol (N-MeFOSE) and is a residual of N-MeFOSE-related chemistry which was used primarily in surface treatment applications (e.g., carpets, textiles). Therefore, PFOSAA and M570 can be considered markers of consumer-related exposure. Both PFOSAA and M570 can metabolize to M556 and PFOSA which, in turn can subsequently metabolize to PFOS. Unlike PFOSAA and M570, M556, PFOSA and PFOS are not specific to any one consumer application. Unlike the other analytes, PFOA and PFHS are not precursors, metabolites or residuals of PFOS. PFOA can be a residual by-product of the production of the POSF-related manufacturing electrochemical fluorination process and was produced by 3M to be an emulsifier in a variety of industrial applications (e.g., ammonium salt) (Olsen et al 2000). PFOA can also be an oxidation product or metabolite of the widely used telomer-based fluorochemicals manufactured by other companies. PFHS, the sulfonate form of perfluorohexane sulfonyl fluoride (PHSF), is a residual by-product of POSF-related products. 3M produced PHSF as a building block compound incorporated in fire fighting foams and specific post-market carpet treatment applications.

## Sample Collection

Through cooperation with the staff of the Adult Changes in Thought (ACT) study, 238 serum samples from elderly adult donors (ages 65-96) equally represented of both sexes were obtained for analysis. Subjects were identified during an enrollment phase of this community-based prospective cohort study of dementia and normal aging conducted collaboratively between the University of Washington and Group Health Cooperative (GHC), a major health maintenance organization in Seattle (McCurry et al 1999). Eligible individuals were those with no known history of neuropsychiatric disease or dementia. Chart reviews of these subjects' GHC medical records were conducted to confirm that the individuals did not reside in nursing homes or have a history of dementia diagnosis in their medical records. Subjects were not excluded from participation in the ACT study on the basis of common age-related chronic illnesses. Although it was desired to obtain more subjects above the age of 80, the study was truncated due to the relatively few subjects who volunteered and were eligible for this age stratum.

## Fluorochemical Analysis

Northwest Bioanalytical (Salt Lake City, Utah) analyzed the serum for the target fluorochemicals using techniques similar to those described by Hansen et al (2001). Details of the specific analytical procedures are presented elsewhere (NWB 2002). Briefly, the analytical method consisted of a liquid:liquid extraction procedure followed by evaporation and reconstitution of the extract residue with 20 mM ammonium acetate in water:20 mM ammonium acetate in methanol (30:70, v/v). The samples were

analyzed by high pressure liquid chromatography/tandem mass spectrometry. Quantitation of the target analytes in serum samples was performed by comparing the chromatographic peak areas for each compound to those generated in a series of extracted calibration standards prepared from control Chinese plasma. The samples were injected in a systematic order. Evaluation of quality control samples injected during each analytical run indicated that the reported quantitative results may differ from the actual concentration by up to 26 percent for all analytes except PFOSA which may have differed by up to 43 percent.

Also presented in this report is a calculated index, total organic fluorine (TOF), which was the percent of each of the seven fluorochemicals' molecular weight that was attributed to organic fluorine [PFOS (64.7%); PFHS (61.9%); PFOA (69.0%); PFOSAA (55.3%); PFOSA (64.7%); M570 (56.6%) and M556 (58.1%)] multiplied by the ppb measured for each fluorochemical and then summed across all seven fluorochemicals.

## Data Analysis

Measures of central tendency applicable to log normally distributed data (median, geometric mean) were used for descriptive analyses. In those instances where a sample was measured below the lower limit of quantitation (LLOQ), the midpoint between zero and the LLOQ was used for calculation of the geometric mean. An assessment of this midpoint assumption and how it affected the calculation of the geometric mean was performed using the 10th and 90th percentile values between zero and the LLOQ for those values <LLOQ.

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In order to minimize parametric assumptions in the estimation of extreme percentiles of the population, the bootstrap method of Efron (1993) was used to generate confidence intervals around the empirical percentiles for serum concentrations. In this method, a large number of replicated estimates of the percentile are generated from full-size samples of the original observations drawn with replacement. The distribution of the deviations of replicates from the original-sample estimate mimics the underlying sampling distribution for the estimate. Bias-corrected, accelerated percentiles were used to minimize residual bias. The bias correction factor is derived by comparing empirical percentiles to bootstrap percentiles and acceleration is accomplished by partial jackknifing.

Twenty-four randomly selected samples, stratified by gender, were split and analyzed to provide an estimate of the reliability of the analyses conducted. The analytical laboratory was blind to the identity of these split samples. These analyses were performed concurrently with all other analyses of the study to minimize experimental error.

RESULTS

The results for the reliability analysis are displayed in Figure 1. None of the PFOSA and most of the M556 split samples were below the LLOQ and are therefore not displayed. There were moderately strong correlations for the split samples ($r = .7$) with either PFOS or PFOA and stronger correlations for PFHS ($r = .9$) and M570 ($r = .8$). The correlation for PFOSAA was less ($r = 0.4$). This was likely due to the fact that only four of the split samples had both values above the LLOQ. Eleven of the split samples had

one of the two values <LLOQ and nine of the split sample analyses for PFOSAA had the identical LLOQ (1.5 ppb). The midpoint between zero and the LLOQ (1.5 ppb) is represented in the graph as the single point below the abscissa (0,0) on the identity (ln y = ln x) line.

Provided in Table 1 is the distribution of the 238 elderly subjects by 10 year age intervals, gender and location. Altogether there were 118 male donors and 120 female donors. As could be expected with the age stratification design used for sample collection, the study subjects' mean ages were comparable by gender: 76.0 years for males and 76.2 years for females. Female subjects had resided, on average, slightly longer in the Seattle area.

The measured concentrations of PFOSA were below the LLOQ (1.0 ppb) for all subjects. For M556, eight subjects had measured serum concentrations above the LLOQ ranging from 2.7 to 4.8 ppb. There were 230 subjects with M556 values <LLOQ (2.5 ppb). Therefore, statistical analyses are not presented for PFOSA and M556 because of the few subjects whose serum concentrations exceeded the LLOQ. Nevertheless, PFOSA and M556 did contribute to the calculation of the TOF index by using, for those values < LLOQ, the midpoint between zero and the LLOQ.

The frequency distributions of the five remaining fluorochemicals, PFOS, PFOA, PFHS, PFOSAA and M570, are displayed in Figure 2. Although the graphs are suggestive of log normal distributions, only the PFOS distribution met such criteria based on the Shapiro-Wilk test. This lack of normality for PFOA, PFHS, PFOSAA and M570 was likely the consequence of a greater percentage of subjects with values <LLOQ for these compounds.

The range, interquartile range, number of samples < LLOQ, cumulative 90th

percentile, median, geometric mean and 95% confidence interval of the geometric mean

for PFOS, PFOA, PFHS, PFOSAA and M570 are provided in Table 2 for all subjects,

males only and females only. Overall, the geometric mean levels of PFOS was 31.0 ppb

(95% CI 28.8-33.4). The range of values was < LLOQ (3.4) to 175.0 ppb. There was no

significant difference (p < .05) between male and female geometric means for any of the

five fluorochemicals reported in Table 2. It should be noted that the geometric mean for

the calculated TOF index was 28.2 ppb (95% CI 26.4 - 30.1) (data not shown). The

calculated TOF index range was 3.7 ppb to 133.1 ppb.

Provided in Figure 3 is a graphical distribution (natural log scale) of the five

fluorochemicals by the three age intervals (65+ thru 75, 75+ thru 85 and 85+ thru 96)

stratified by gender. The box covers the interquartile range of the natural log distribution.

The circle within the box is the mean. The whiskers extend to the last observation within

1.5 times the interquartile range. The dots with lines through them represent observations

outside the 1.5 times interquartile range. In simple linear regression analyses, age was

significantly (p < .05) negatively associated with PFOS and PFOA among elderly men

but only with PFOA among women. Age was not significantly associated with PFHS,

PFOSAA or M570 in either sex.

There was a weak correlation between age and years residence in the Seattle area

(r = 0.2). Analyzed independently of age, there were no significant associations between

years resided in the Seattle area and PFOS, PFOA, PFHS, PFOSAA or M570.

As discussed previously, the geometric mean data were calculated under the

assumption that, for individual serum fluorochemical values <LLOQ, the midpoint

between zero and the LLOQ was assigned. For PFOS, only one subject had a value

<LLOQ (3.4 ppb)) and only five subjects were below the LLOQ (1.4 ppb) for PFOA;

thus this assumption did not affect the calculation of the geometric means for these two

fluorochemicals. However, considerably more subjects had values less than the LLOQs

for PFHS, PFOSAA and M570 (see Table 2). If these values were assumed to be 10% or

90% of this range between zero and the LLOQ, the respective range of the geometric

means (95% confidence interval in parenthesis) became: PFHS 1.5 ppb (1.2-1.8) to 2.5

ppb (2.3-2.7); PFOSAA 0.7 ppb (0.6-0.9) to 2.1 ppb (1.9-2.2) and M570 0.7 ppb (0.6-0.8)

to 1.5 ppb (1.4-1.6). These geometric mean values were not substantially different than

those calculated using the midpoint between zero and the <LLOQ as presented in Table

2. Consequently, the midpoint between zero and the LLOQ was used for the analyses.

Scatter plots (log scale) between the five fluorochemicals are displayed in Figure

4. PFOS and PFOA were highly correlated ($r = .75$). PFOS had a lower, but similar,

correlation with PFOSAA and PFHS ($r = .42$) and lower yet with M570 ($r = .29$). The

correlation between PFOSAA and M570 was weak ($r = .17$). The remaining scatter plot

displays the correlation between PFOA and PFHS ($r = 0.36$). Both PFOSAA and M570

were significant predictors of PFOS in a multivariable model adjusted for age, gender and

their interaction (Table 3). PFOSAA was the stronger of the two independent variables.

Seventy-five percent of the variation of PFOS was left unexplained. In other models,

PFHS and PFOA remained significant predictors of PFOS after adjustment for age,

gender and their interaction terms (Tables 4 and 5). None of the models (Tables 3

through 5) had lack of fit F ratios that were statistically significant ($p < .05$).

Presented in Table 6 are the results from bootstrap analyses conducted to provide

tolerance limits. The tolerance limits represent the limit of each fluorochemical within

which the stated proportion of the population is expected to be found. Presented are the

mean values of the five serum fluorochemicals and TOF for the 90th, 95th and 99th percent

tolerance limits along with the upper limit (bound) from the 95% confidence interval.

For example, the mean of the 95% tolerance limit for PFOS was 84.1 ppb with an upper

95% percent confidence limit of 104.0 ppb. At the lowest tolerance limit analyzed,

(90%), the mean for PFOS was 61.1 ppb with an upper 95% confidence limit of 71.3 ppb.

At the highest tolerance limit analyzed, (99%), the mean was 133.4 ppb with an upper

95% confidence limit of 169.7 ppb. For other fluorochemicals analyzed, the mean of the

95% tolerance limit for PFOA was 9.7 ppb with an upper 95% confidence limit of 11.3

ppb. For PFHS, the mean of the 95% tolerance limit was 8.3 ppb with an upper 95%

confidence limit of 10.3 ppb. The mean of the 95% tolerance limit for PFOSAA was 7.8

ppb with an upper 95% confidence limit of 10.7 ppb. For M570, the mean 95% tolerance

limit was 3.8 ppb with an upper 95% confidence limit of 4.3 ppb. Finally, for the

calculated index of TOF, the mean was 70.2 ppb for the 95% tolerance limit with an

upper 95% confidence limit of 81.2 ppb.


DISCUSSION

The findings from this analysis of serum fluorochemical concentrations in the sera

of 238 elderly subjects are consistent, albeit slightly lower, than the findings reported in

a companion 3M report which examined serum fluorochemical levels in 645 American

Red Cross (ARC) blood donors (Olsen et al 2002). These geometric mean comparisons

(ARC vs elderly) were (95% CI in parentheses): PFOS 34.9 ppb (33.3-36.5) vs 31.0 ppb (28.8-33.4); PFOA 4.6 ppb (4.3-4.8) vs 4.2 ppb (3.9-4.5); PFHS 1.9 ppb (1.8-2.0) vs 2.2 ppb (2.0-2.4); PFOSAA 2.0 ppb (1.9-2.1) vs 1.5 ppb (1.4-1.7); and M570 1.3 ppb (1.3-1.4) vs 1.2 ppb (1.1-1.3). The 95% tolerance limits and their upper bounds were also comparable between the two study populations (ARC vs elderly): PFOS 88.5 ppb (upper 95% CI interval = 100.0 ppb) vs 84.1 ppb (104.4); PFOA 12.1 ppb (13.6) vs 9.7 ppb (11.3); PFHS 9.5 ppb (10.8) vs 8.3 ppb (10.3); PFOSAA 7.6 ppb (8.5) vs 7.8 ppb (10.7); and M570 5.0 ppb (5.4) vs 3.8 ppb (4.3). Among other limited samples obtained within the United States, mean serum PFOS concentrations in humans have been reported to be 30 ppb in 18 pooled blood banks, 44 ppb from a pooled commercial sample of 500 donors, 33 ppb from a different pooled commercial sample of 200 donors and 28 ppb in 65 commercial individual human sera samples (3M Company 2000; Hansen et al 2001). The findings of this study were also comparable to a very limited number of European samples which found mean serum PFOS concentrations at 17 ppb in 5 pooled samples from a Belgium blood bank, 53 ppb in 6 pooled samples from the Netherlands, 37 ppb from 6 pooled blood samples from Germany and between <LLOQ 3.2 ppb and 85 ppb in 39 individual Swedes (3M Company, 2000).

The geometric mean calculated TOF index in the present study of elderly subjects (28.2 ppb, 95% CI 26.4 - 30.1) was also consistent with that calculated among the ARC blood donors (31.7 ppb, 95% CI 30.4 - 33.0). It was also comparable with measurements of low ppb total organic fluorine concentrations reported in a limited number of general population samples since the late 1960's using a variety of analytical methods (Taves 1968; Taves et al 1976; Singer and Ophaug 1979; Belisle 1981).

There was a strong correlation between PFOS and PFOA which was consistent with the companion research performed on ARC blood donors (Olsen et al 2002). Whereas PFOS has been routinely measured in human populations, wildlife, marine mammals and piscivorous birds (Geisy and Kannan 2001; Kannan et al 2001a; 2001b; Hansen et al 2001), serum PFOA concentrations, to date, have been consistently quantified (i.e., measured above the LLOQs) primarily in humans. This association is of significant interest because PFOA cannot convert to PFOS (or vice versa). Whether this association is due to the presence of PFOA as a by-product in POSF-related materials or other non-related environmental exposures or consumer products from other manufacturers(e.g., higher carbon telomers) remains to be explained. Another unanswered question is whether perfluorooctanesulfonamide residuals may metabolize in humans to PFOA as this could explain the strong association observed in this study along with the fact that both PFOS and PFOA are suspected to have long serum half-lives in humans, 8.7 years (SD = 6.1) and 4.4 years (SD = 3.5), respectively (Burris et al 2002).

PFOS was associated with two fluorochemicals, PFOSAA and M570, known to be analytes from exposure to consumer products involving paper/packaging and carpet/textile protectants, respectively. Overall, the data, to date, reveal PFOS bioaccumulation in animals may be primarily through environmental sources whereas both environmental and consumer product exposures likely contribute to serum PFOS concentrations in humans.

As with any interpretation of data obtained from a study population, questions arise regarding the representativeness and ability to generalize the data collected. Historically, the ACT study has reported a volunteer participation rate of 58 percent

(McCurry et al, 1999). Of those who have participated, 65 percent were found to be cognitively intact subjects and agreed to participate in the longitudinal portion of the ACT study. Thus, 38 percent of the GHC members, eligible by age ($\geq$65), eventually participated in the ACT study. We are unaware of any database that can be considered generalizable to the diverse United States elderly population without measures of random and systematic bias incorporated in the data analysis.

We did notice a decline in measured PFOS concentrations with age among elderly men but not women. This was not observed in the ARC blood donor study which examined subjects in the age range 20-69. It is possible that this may be due to less potential for environmental or non-occupational exposures among the most elderly. Unlike the ARC blood donors, we did not observe a significant difference in PFOS levels by gender (albeit such differences were not large in the ARC study).

Given the consistency of the data analyzed, to date, we hypothesize that the average serum PFOS concentrations in non-occupational adult populations likely ranges between 30 to 40 ppb with 95% of a population's serum PFOS concentrations below 100 ppb. Understanding these serum PFOS concentrations in human populations will be useful in risk characterization since serum PFOS likely reflects cumulative human exposure. Currently available data (unpublished reports to U.S. EPA:Docket No. FYI-0500-01378) suggest that the serum concentrations observed in humans are substantially less than those required to cause adverse effects in laboratory animals (3M Company 2000).

## ACKNOWLEDGEMENTS

# REFERENCES

3M Company (2000). SIDS Initial Assessment Report Perfluorooctane Sulfonic Acid and its Salts. St. Paul:3M Company, September 20, 2000.

Belisle J (1981). Organic fluorine in human serum: natural versus industrial sources. Science 212:1509-1510.

Burris JM, Lundberg JK, Olsen GW, Simpson C, Mandel JH (2002). Interim Report: Determination of serum half-lives of several fluorochemicals. St. Paul:3M Company, January 11, 2002.

Efron B, Tibshiarani RJ. An Introduction to the Bootstrap. In: Cox DR, Hinkley DV, Reid N, Rubin DB, Silverman BW, eds. Monographs on Statistics and Applied Probability. Vol 57 New York:Chapman H Hall.

Giesy JP, Kannan K (2001). Global distribution of perfluorooctane sulfonate in wildlife. Environ Sci Technol 35(7):1339-1342.

Hansen KJ, Clemen LA, Ellefson ME, Johnson HO (2001a). Compound-specific quantitative characterization of organic fluorochemicals in biological matrices. Environ Sci Technol 35:766-770.

Kannan K. Koistenen J, Beckmen K, Evans T, Gorzelany JF, Hansen KJ, Jones PD, Helle E. Nyman M, Giesy JP (2001b). Accumulation of perfluorooctane sulfonate in marine mammals. Environ Sci Technol 35(8):1593-1598.

Kannan K, Franson JC, Bowerman WW, Hansen KJ, Jones PD, Giesy JP (2001). Perfluorooctane Sulfonate in fish-eating water birds including bald eagles and albatrosses. Environ Sci Technol 35(15):3065-3070.

McCurry SM, Edland SD, Teri L, Kukull WA, Bowen JD, McCormick WC, Larson EB (1999). The cognitive abilities screening instrument (CASI): Data from a cohort of 2524 cognitively intact elderly. Int J Geriatric Psych 14:882-888.

Northwest Bioanalytical (NWB, 2002). Quantitative determination of PFOS and related compounds in human serum by LC/MS/MS January 10, 2002.

Olsen GW. Burris JM, Mandel JH, Zobel LR (1999). Serum perfluorooctane sulfonate and hepatic and lipid clinical chemistry tests in fluorochemical production employees. JOEM 41:799-806.

Olsen GW, Burris JM, Lundberg JK, Hansen KJ, Mandel JH, Zobel LR (2002). Identification of fluorochemicals in sera of American Red Cross blood donors. St. Paul:3M Company (unpublished report).

Singer L, Phaug RH (1979). Concentrations of ionic, total, and bound fluoride in plasma. Clin Chem 25:523-525.

Taves D (1968). Evidence that there are two forms of fluoride in human serum. Nature 217:1050-1051.

Taves D, Guy W, Brey W (1976). Organic fluorocarbons in human plasma: Prevalence and characterization. In: Filler R, eds. Biochemistry Involving Carbon-Fluorine Bonds. Washington DC:American Chemical Society, pp 117-134.

Table 1
Distribution of Elderly Adult Subjects by Age, Years Lived in Seattle and Gender

|  | Male | Female | All |
|---|---|---|---|
| Number | 118 | 120 | 238 |
| Age - Number (%) |  |  |  |
| 65+ thru 75 | 61 (52) | 60 (50) | 121 (51) |
| 75+ thru 85 | 46 (39) | 47 (39) | 93 (39) |
| 85+ thru 96 | 11 (9) | 13 (11) | 24 (10) |
| Average Age (S.D.) | 76.0 ( 7.0) | 76.2 (6.4) | 76.1 (6.7) |
| Years Lived in Seattle Area (S.D.) | 50.2 (20.1) | 53.3 (17.7) | 51.8 (18.9) |

Table 2

Measures of Central Tendency of Serum Fluorochemicals for All Elderly Subjects (N = 238) and by Gender

|  | PFOS | PFOA | PFHS | PFOSAA | M570 |
|---|---|---|---|---|---|
| **All (N = 238)** |  |  |  |  |  |
| Range | <LOQ (3.4) – 175.0 | <LOQ (1.4) – 16.7 | <LOQ (1.4) – 40.3 | <LOQ (1.6) – 21.1 | <LOQ (1.0) – 6.6 |
| Q1 – Q3 | 21.6 – 44.8 | 3.1 – 6.0 | 1.4 – 3.7 | <LOQ (1.6) – 2.5 | <LOQ (1.0) – 2.0 |
| <LOQ (N) | <3.4 (1) | <1.4 (5) | <1.4 (58) | <1.6 (115) | <1.0 (83) |
| Cumulative 90% | 61.3 | 7.8 | 6.4 | 5.3 | 3.0 |
| Median | 30.2 | 4.2 | 2.3 | 1.6 | 1.3 |
| Geometric Mean | 31.0 | 4.2 | 2.2 | 1.5 | 1.2 |
| 95% C.I. Geometric Mean | 28.8 – 33.4 | 3.9 – 4.5 | 2.0 – 2.4 | 1.4 – 1.7 | 1.1 – 1.3 |
| **Males (N = 118)** |  |  |  |  |  |
| Range | <LOQ (3.4) – 161.0 | <LOQ (1.4) – 14.2 | <LOQ (1.4) – 40.3 | <LOQ (1.5) – 19.0 | <LOQ (1.0) – 6.6 |
| Q1 – Q3 | 22.3 – 44.2 | 3.0 – 5.3 | 1.4 – 3.7 | <LOQ (1.5) – 2.2 | <LOQ (1.0) – 2.1 |
| <LOQ (N) | <3.4 (1) | <1.4 (2) | <1.4 (28) | <1.5 (58) | <1.0 (34) |
| Cumulative 90% | 57.1 | 7.4 | 6.5 | 4.3 | 2.9 |
| Median | 30.3 | 4.0 | 2.5 | 1.5 | 1.4 |
| Geometric Mean | 30.2 | 4.0 | 2.3 | 1.4 | 1.3 |
| 95% C.I. Geometric Mean | 27.2 – 33.5 | 3.7 – 4.4 | 1.9 – 2.6 | 1.3 – 1.6 | 1.1 – 1.5 |

**Females (N = 120)**

| | | | | | |
|---|---|---|---|---|---|
| Range | 9.6 – 175.0 | <LOQ (1.4) – 16.7 | <LOQ (1.4) – 17.5 | <LOQ (1.6) – 21.1 | <LOQ (1.0) – 5.1 |
| Q1 – Q3 | 20.4 – 45.4 | 3.2 – 6.4 | <LOQ (1.4) – 3.7 | <LOQ (1.6) – 2.7 | <LOQ (1.0) – 1.9 |
| <LOQ (N) | - | <1.4 (3) | <1.4 (30) | <1.6 (57) | <1.0 (49) |
| Cumulative 90% | 73.5 | 8.7 | 6.5 | 5.6 | 3.2 |
| Median | 30.0 | 4.3 | 2.1 | 1.6 | 1.2 |
| Geometric. Mean | 31.9 | 4.4 | 2.1 | 1.6 | 1.1 |
| 95% C.I. Geometric Mean | 28.6 – 35.6 | 4.0 – 4.9 | 1.8 – 2.5 | 1.4 – 1.9 | 1.0 – 1.3 |

Table 3
Multivariable Regression Model of PFOS[*] by PFOSAA[*], M570[*],
Age, Gender and Age x Gender Interaction

|  | Coefficient | SE | t ratio | p value |
|---|---|---|---|---|
| Intercept | 4.3 | 0.38 | 11.3 | < .0001 |
| PFOSAA[*] | 0.3 | 0.04 | 6.8 | < .0001 |
| M570[*] | 0.2 | 0.05 | 3.7 | .0003 |
| Age | - 0.01 | 0.005 | -2.7 | .008 |
| Gender | - 0.3 | 0.38 | -0.9 | .35 |
| Age x Gender | 0.005 | 0.005 | 1.0 | .32 |

N = 238

* Natural log

Adjusted $r^2 = 0.25$

Gender: females = 1; males = 0

t ratio = coefficient/SE (standard error)

Table 4
Multivariable Regression Model of PFOS[*] by PFOA[*]
Age, Gender and Age x Gender Interaction

|  | Coefficient | SE | t ratio | p value |
|---|---|---|---|---|
| Intercept | 2.2 | 0.3 | 7.0 | < .0001 |
| PFOA[*] | 0.8 | 0.05 | 16.8 | < .0001 |
| Age | - 0.0002 | 0.004 | -0.1 | .96 |
| Gender | - 0.2 | 0.3 | -0.7 | .47 |
| Age x Gender | 0.003 | 0.004 | 0.7 | .50 |

N = 238

* Natural log

Adjusted $r^2 = 0.56$

Gender: females = 1; males = 0

t ratio = coefficient/SE (standard error)

Table 5
Multivariable Regression Model of PFOS* by PFHS*
Age, Gender and Age x Gender Interaction

|  | Coefficient | SE | t ratio | p value |
|---|---|---|---|---|
| Intercept | 4.3 | 0.4 | 10.7 | < .0001 |
| PFHS* | 0.3 | 0.04 | 6.9 | < .0001 |
| Age | - 0.01 | 0.005 | -2.6 | .01 |
| Gender | - 0.2 | 0.4 | -0.5 | .63 |
| Age x Gender | 0.003 | 0.005 | 0.6 | .57 |

N = 238

* Natural log

Adjusted $r^2 = 0.19$

Gender: females = 1; males = 0

t ratio = coefficient/SE (standard error)

Table 6
Tolerance Limits and Their Associated Means and Upper 95th Percent Confidence Limits
for Serum Fluorochemicals and Calculated Total Organic Fluorine Index

|  | Tolerance Level | Mean | Upper 95th Percent Confidence Limit |
|---|---|---|---|
| PFOS | 90% | 61.1 | 71.3 |
|  | 95% | 84.1 | 104.0 |
|  | 99% | 133.4 | 169.7 |
| PFOA | 90% | 7.9 | 9.0 |
|  | 95% | 9.7 | 11.3 |
|  | 99% | 14.3 | 16.2 |
| PFHS | 90% | 6.3 | 7.2 |
|  | 95% | 8.3 | 10.3 |
|  | 99% | 16.3 | 29.6 |
| PFOSAA | 90% | 5.1 | 6.1 |
|  | 95% | 7.8 | 10.7 |
|  | 99% | 16.3 | 20.3 |
| M570 | 90% | 3.0 | 3.4 |
|  | 95% | 3.8 | 4.3 |
|  | 99% | 5.7 | 6.5 |
| TOF | 90% | 52.5 | 58.2 |
|  | 95% | 70.2 | 81.2 |
|  | 99% | 104.9 | 127.6 |

Figure 1.  Analysis of Split Samples for Reliability Assessment of PFOS, PFOA, PFHS, PFOSAA and M570
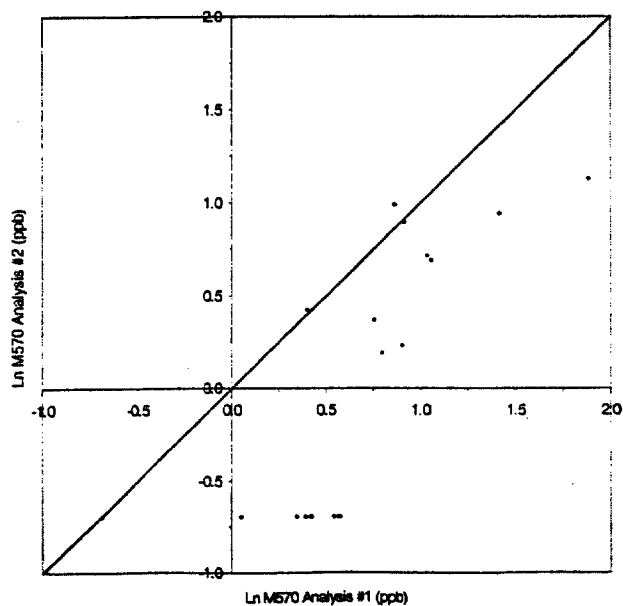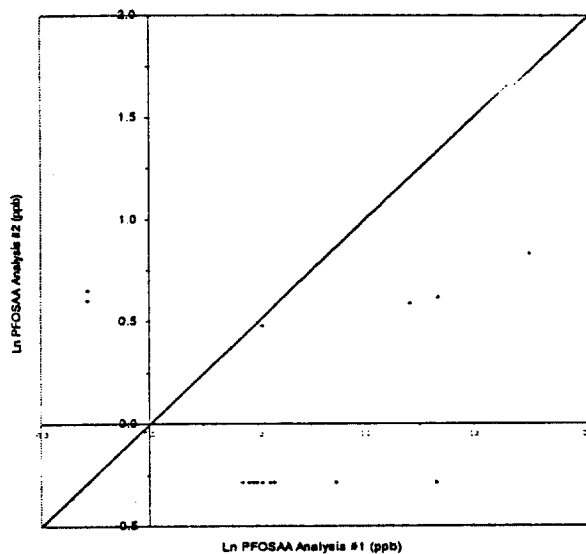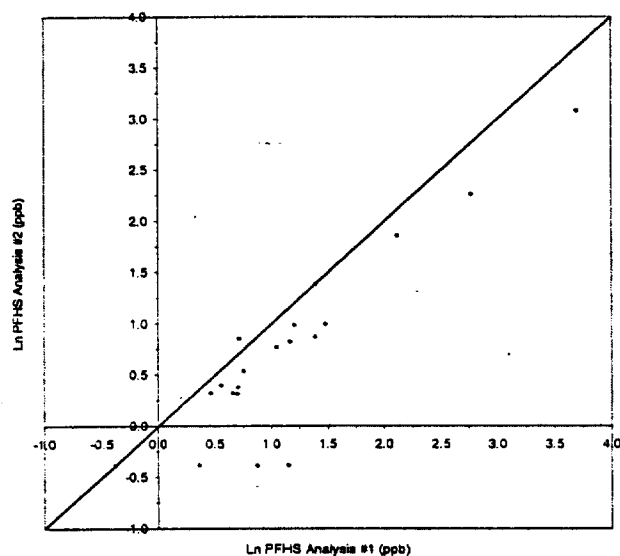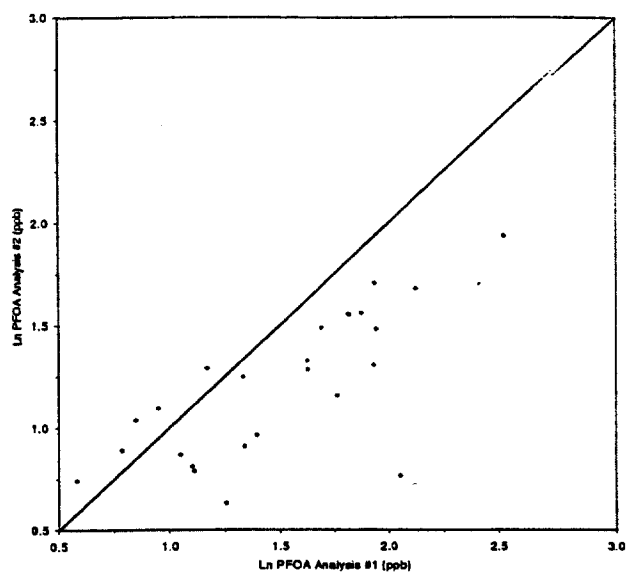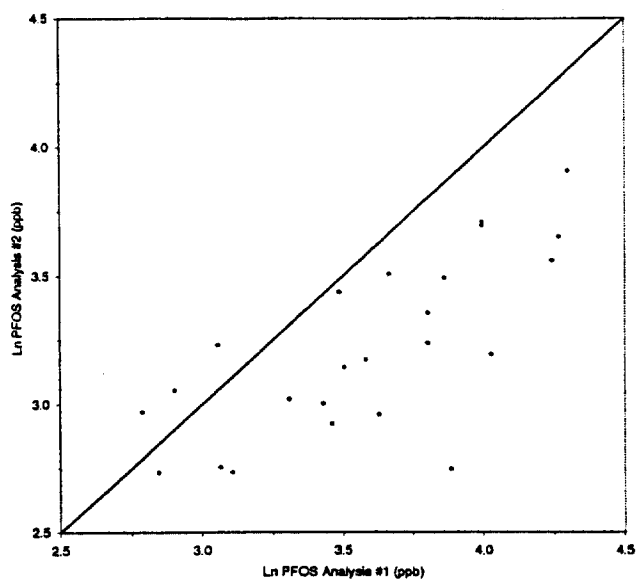
Figure 2. Elderly Study Poulation Distribution of Measured Fluorochemical Concentrations
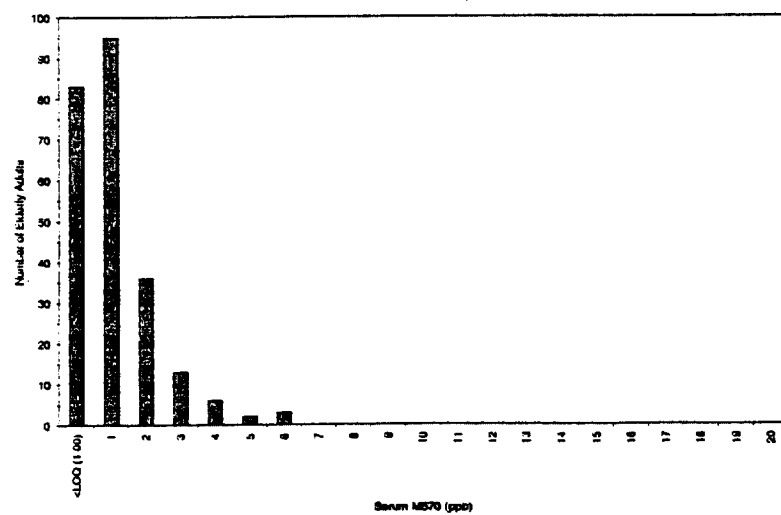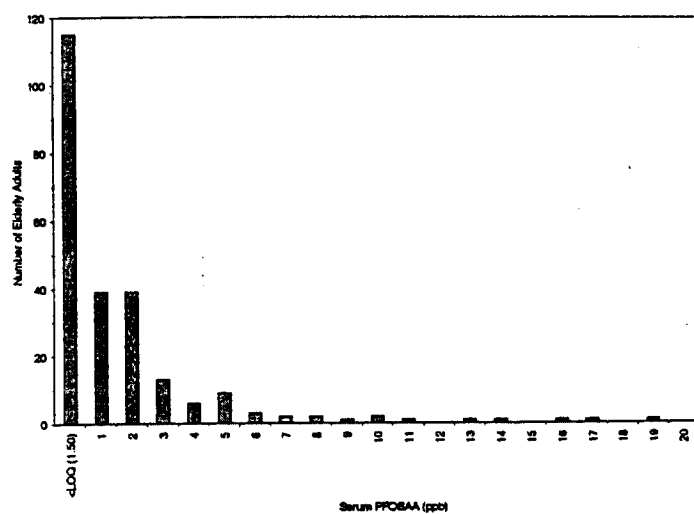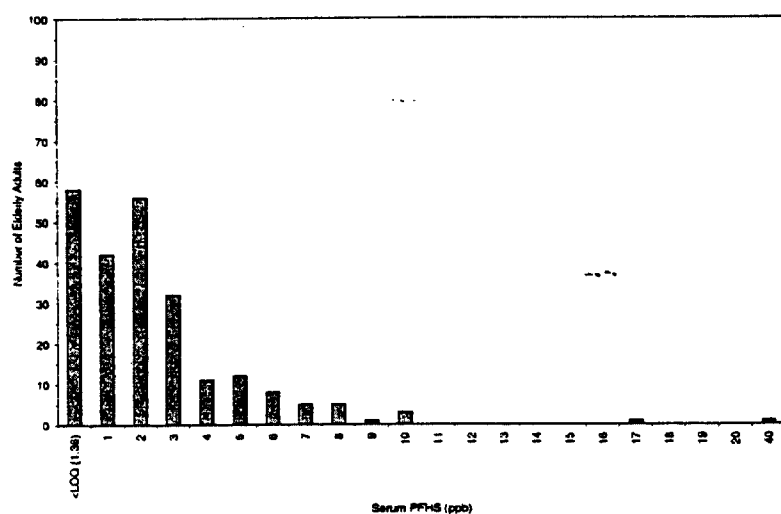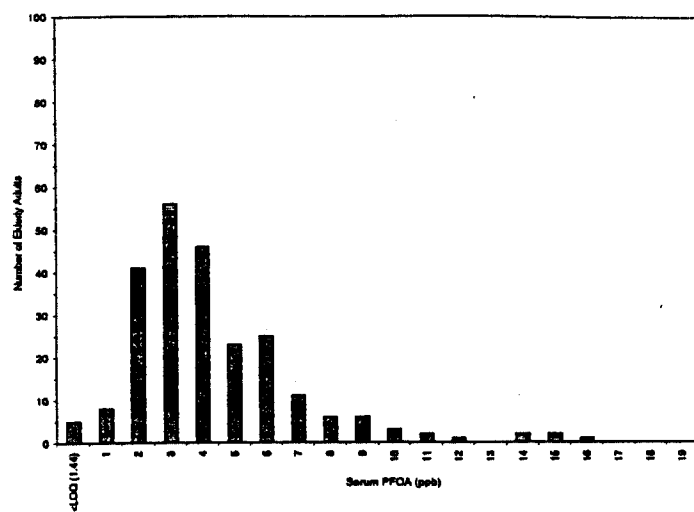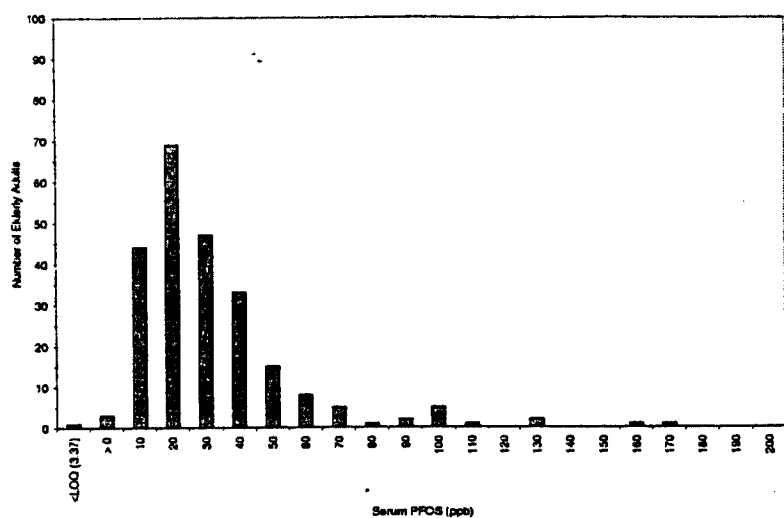
Figure 3. Box and Whisker Plots of Serum Fluorochemical Concentrations (ppb) by Age and Gender
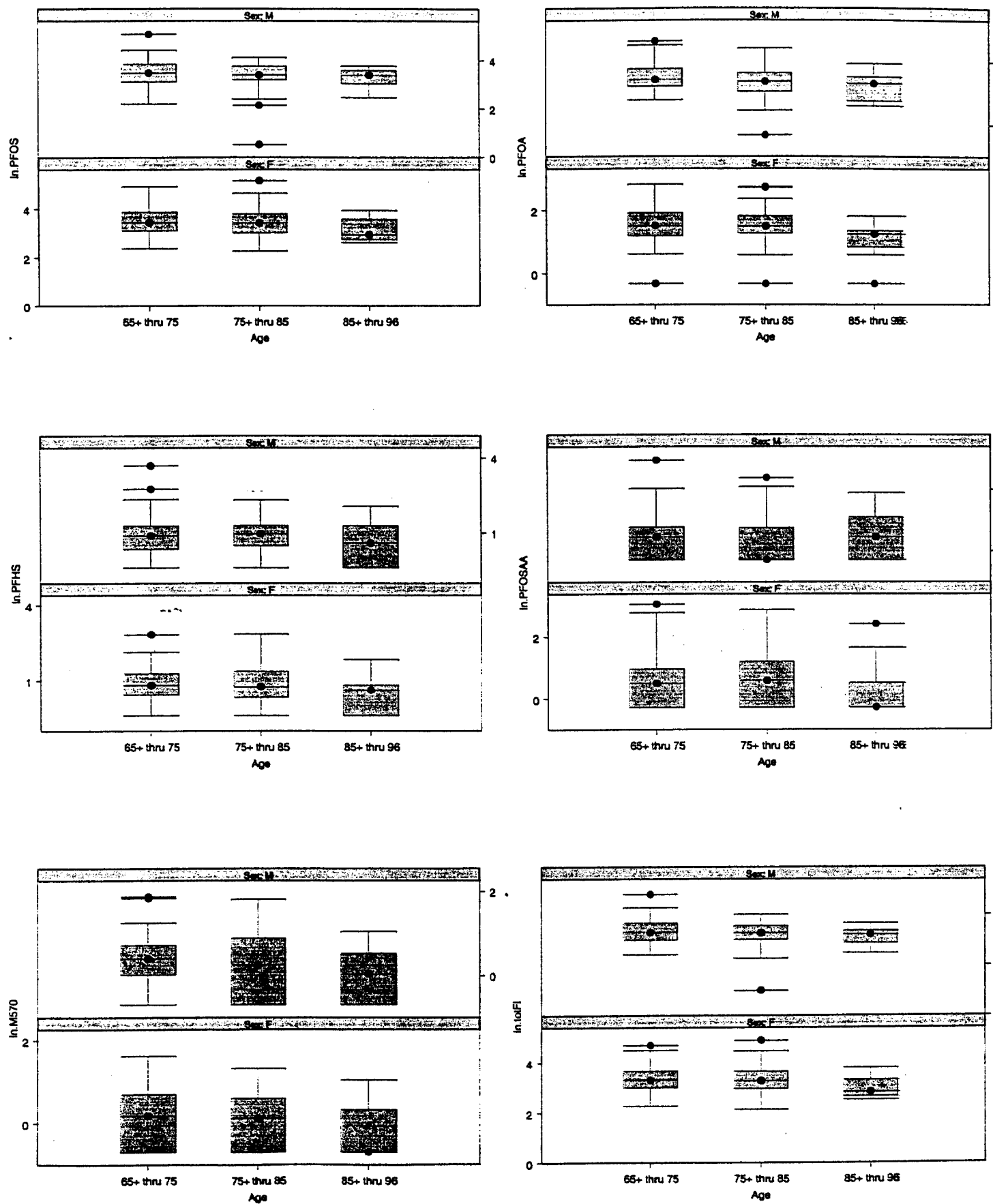
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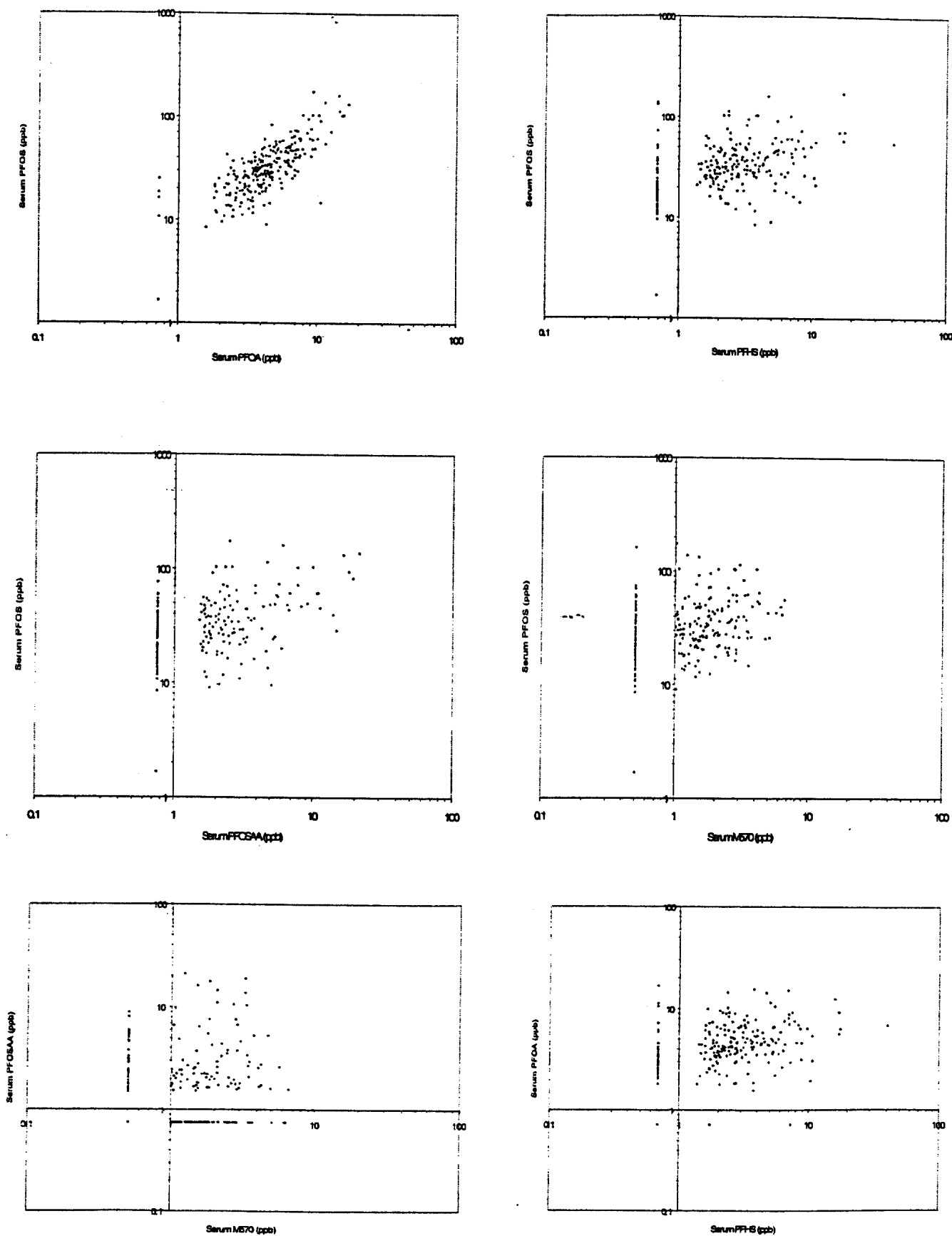
# FINAL REPORT
### Epidemiology
### Medical Department
### 3M Company
### St. Paul, MN  55144

Date: March 15, 2002

Title: Identification of Fluorochemicals in Human Sera.  III. Pediatric Participants in a Group A Streptococci Clinical Trial Investigation

Study
Start Date:     September 29, 2000

Protocol Number EPI-0011

Principal Investigator:                    Geary W. Olsen, D.V.M., Ph.D.[1]

3M Co-investigators:                       Jean M. Burris, M.P.H., R.N.[1]
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Study Sponsor:                             Corporate Occupational Medicine, Medical Department, 3M Company, 220-3W-05, St. Paul, MN  55144

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## ABSTRACT

The purpose of this study was to better characterize the distribution of seven

fluorochemicals, including perfluorooctanesulfonate (PFOS, $C_8F_{17}SO_3^-$) in 599 pediatric

samples obtained from a multi-center clinical trial of group A streptococcal infections.

Serum samples were collected in 1994-1995 and frozen at -20 degrees Celsius. The

samples were void of personal identifiers. The only known demographic factors were:

age (2-12), gender and the state residence (n = 23 states and the District of Columbia).

Sera samples were extracted and quantitatively analyzed for seven fluorochemicals

using high-pressure liquid chromatography/electrospray tandem mass spectrometry. The

seven fluorochemicals were perfluorooctanesulfonate (PFOS, $C_8F_{17}SO_3^-$); N-ethyl

perfluorooctanesulfonamidoacetate (PFOSAA, $C_8F_{17}SO_2N(CH_2CH_3)CH_2COO^-$); N-

methyl perfluorooctanesulfonamidoacetate (M570, $C_8F_{17}SO_2N(CH_3)CH_2COO^-$);

perfluorooctanesulfonamidoacetate (M556, $C_8F_{17}SO_2N(CH)CH_2COO^-$);

perfluorooctanesulfonylamide (PFOSA, $C_8F_{17}SO_2NH_2$); perfluorooctanoate (PFOA,

$C_7F_{13}COO^-$); and perfluorohexanesulfonate (PFHS, $C_6F_{13}SO_3^-$).

Overall, the geometric mean measured concentration of PFOS was 37.5 ppb (95% CI

33.3-36.5). The measured PFOS concentrations ranged from 6.7 ppb to 515.0 ppb. Male

children had a significantly (p < .01) higher geometric mean serum PFOS level

compared to female children [male children geometric mean = 40.1 ppb (95% CI 37.7-

42.6) vs female geometric mean = 35.2 ppb (95% CI 33.3-37.2)]. Bootstrap analysis was

used to calculate a mean 95% tolerance limit of 88.5 ppb with an upper 95% confidence

limit of 97.0 ppb. Additional geometric mean and tolerance limit data are reported for

PFOA, PFHS, PFOSAA and M570. A unique finding observed in these pediatric data

that was not observed in the adult or elderly data reported elsewhere, were the higher

95% tolerance limit mean concentrations for PFHS (64.5 ppb) and M570 (11.9 ppb) with

upper 95% confidence limits of 80.6 ppb and 14.8 ppb, respectively. It is unlikely that

these findings are a consequence of analytical systematic error between these three

studies. There was a strong correlation between PFOS and both PFOA (r = .70) and

PFHS (r = .66) with lower correlations with PFOSAA (r = .43) and M570 (r = .42). The

number of samples with measured concentrations of PFOSA and M556 less than the

LLOQ prohibited meaningful statistical analyses for these compounds.

The findings from this analysis of serum PFOS concentrations are consistent with

serum PFOS levels of 645 American Red Cross blood donors and 238 elderly subjects

from a longitudinal study of cognitive function. Along with other human data, the

average serum PFOS concentration in non-occupational human populations may

approximate 30 to 40 ppb with 95% of the population's serum PFOS concentrations

below 100 ppb. Since serum PFOS concentration likely reflects cumulative human

exposure, this information will be useful for risk characterization. The higher mean 95%

tolerance limits for PFHS and M570 suggest that some children may have had a greater

exposure experience than adults and the elderly to products containing

perfluorohexanesulfonyl fluoride (PHSF) and N-methyl

perfluorooctanesulfonamidoethanol (N-MeFOSE) surface protectants.

INTRODUCTION

In May, 2000 the 3M Company (3M) announced that it would voluntarily cease manufacturing perfluorooctanesulfonyl- (POSF, $C_8F_{17}SO_2F$) related materials after the compound, perfluorooctanesulfonate (PFOS, $C_8F_{17}SO_3^-$), was found to be pervasive and persistent in human populations, wildlife, marine mammals and piscivorous birds (3M Company 2000; Hansen et al 2001; Giesy and Kannan 2001; Kannan et al 2001a; 2001b). POSF, produced by an electrochemical fluorination process, is used as the basic building block to create unique chemistries through the sulfonyl fluoride moiety using conventional hydrocarbon reactions. For example, POSF can be reacted with methyl or ethyl amines to produce either N-ethyl or N-methyl perfluorooctanesulfonamide. At this stage, these intermediates can be used to make amides, oxazolidinones, silanes, carboxylates and alkoxylates as commercial products. Also, these intermediates can be subsequently reacted with ethylene carbonate to form either N-ethyl or N-methyl perfluorooctanesulfonamidoethanol which can be used to make adipates, phosphate esters, fatty acid esters, urethane co-polymers and acrylates as commercialized products. Depending upon the specific functional derivatization or the degree of polymerization, such POSF-based products may degrade or metabolize, to an undetermined degree, to PFOS, a stable and persistent end-product that has the potential to bioaccumulate. While not a major commercial product, PFOS itself has been used in some products, including fire fighting foams.

The mechanisms and pathways leading to the presence of PFOS in human blood are not well characterized but likely involve environmental exposure to PFOS or its precursor molecules and residual levels of PFOS or PFOS precursors in industrial and commercial

products. PFOS has been detected at low parts per billion (ppb) concentrations in the general population (Hansen et al 2001; 3M Company 2000) although the scope of these investigations has been limited. Using high pressure liquid chromatography/electrospray tandem mass spectrometry, Hansen et al (2001) detected an average PFOS concentration of 28.4 ppb (SD 13.6; range 6.7-81.5) in 65 commercial individual human sera samples. An analysis of pooled blood samples (n = 3 to 6 pooled samples per location with 5 to 10 donors per pooled sample) from 18 blood banks in the United States resulted in a mean measured PFOS serum concentration of 30 ppb with a range from 9 to 56 ppb (3M Company, 2000). Serum PFOS concentrations among production employees working in POSF-related processes were approximately 2 parts per million (ppm) depending on work activity (range 0.1 to 12 ppm) (Olsen et al 1999).

The purpose of this study was to better characterize the distribution of seven fluorochemicals, including PFOS and some of its precursors, using individual pediatric samples obtained from a multi-center clinical trial of group A streptococcal infections. The present study is the third formal assessment undertaken by the 3M Company to examine the distribution of PFOS in human sera. The previous two assessments examined serum fluorochemical levels among American Red Cross adult blood donors (Olsen et al 2000a) and elderly participants of a longitudinal cognitive function study in the Seattle (WA) area (Olsen et al 2000b).

METHODS

## Fluorochemicals

The seven analytes detected and quantified in this study were: PFOS; N-ethyl perfluorooctanesulfonamidoacetate (PFOSAA, $C_8F_{17}SO_2N(CH_2CH_3)CH_2COO^-$); N-methyl perfluorooctanesulfonamidoacetate (M570, $C_8F_{17}SO_2N(CH_3)CH_2COO^-$); perfluorooctanesulfonamido acetate (M556, $C_8F_{17}SO_2N(CH)CH_2COO^-$); perfluorooctanesulfonylamide (PFOSA, $C_8F_{17}SO_2NH_2$); perfluorooctanoate (PFOA, $C_7F_{13}COO^-$); and perfluorohexanesulfonate (PFHS, $C_6F_{13}SO_3^-$).

PFOSAA is an oxidation product of N-ethyl perfluorooctanesulfonamidoethanol (N-EtFOSE) and is a residual in N-EtFOSE-related chemistry which was primarily used in paper and packaging protectant applications. M570 is an oxidation product of N-methyl perfluorooctanesulfonamidoethanol (N-MeFOSE) and is a residual of N-MeFOSE-related chemistry which was used primarily in surface treatment applications (e.g., carpets, textiles). Therefore, PFOSAA and M570 can be considered markers of consumer-related exposure. Both PFOSAA and M570 can metabolize to M556 and PFOSA which, in turn can subsequently metabolize to PFOS. Unlike PFOSAA and M570, M556, PFOSA and PFOS are not specific to any one consumer application. Unlike the other analytes, PFOA and PFHS are not precursors, metabolites or residuals of PFOS. PFOA can be a residual by-product of the production of the POSF-related manufacturing electrochemical fluorination process and was produced by 3M to be an emulsifier in a variety of industrial applications (e.g., ammonium salt) (Olsen et al 2000). PFOA can also be an oxidation product or metabolite of the widely used telomer-based

fluorochemicals manufactured by other companies. PFHS, the sulfonate form of perfluorohexane sulfonyl fluoride (PHSF) may be a residual by-product of POSF-related production. 3M produced the PHSF as a building block compound incorporated in fire fighting foams and specific post-market carpet treatment applications.

Sample Collection

The sera analyzed in this study were collected as part of a large multi-center clinical trial of 1,131 children, ages 2 to 12 years, who presented with signs and symptoms of acute-onset pharyngitis (Kaplan et al 1998). All 1,131 children had positive throat cultures for group A streptococci at an initial visit. The objective of the original research was to determine age-specific geometric mean titers and upper limits of normal for antistreptolysin O and anti-deoxyribonuclease B. Sera for the clinical trial were obtained between January 1994 and March 1995. Sera were kept frozen at -20 degrees Celsius by the University of Minnesota Department of Pediatrics prior to the 3M request of an alloquot of 0.1 ml per sample for the present study (additional amounts were obtained for the reliability analysis - see below). Because of the uncertainty regarding the population distribution of PFOS, sample size was estimated by the use of tolerance limits (Natrella 1966). Provided below is the sampling distribution that was used. Percent sampled was the highest for the younger ages and included all samples four years of age and less.

| Age Group | Total N | Sampled (%) |
|---|---|---|
| 2 | 27 | 27 (100) |
| 3 | 51 | 51 (100) |
| 4 | 81 | 81 (100) |
| 5 | 122 | 100 (82) |
| 6 | 146 | 80 (55) |
| 7 | 161 | 60 (37) |
| 8 | 131 | 40 (31) |
| 9 | 135 | 40 (30) |
| 10 | 109 | 40 (37) |
| 11 | 87 | 40 (46) |
| 12 | 81 | 40 (49) |
| Total | 1131 | 599 (53) |

Fluorochemical Analysis

Northwest Bioanalytical (Salt Lake City, Utah) analyzed the serum for the target

fluorochemicals using techniques similar to those described by Hansen et al (2001).

Details of the specific analytical procedures are presented elsewhere (NWB 2002).

Briefly, the analytical method consisted of a liquid:liquid extraction procedure followed

by evaporation and reconstitution of the extract residue with 20 mM ammonium acetate

in water:20 mM ammonium acetate in methanol (30:70, v/v). The samples were

analyzed by high pressure liquid chromatography/tandem mass spectrometry.

Quantitation of the target analytes in the serum samples was performed by comparing the

chromatographic peak areas for each compound to those generated in a series of extracted

calibration standards prepared from control Chinese plasma. The samples were injected

in a systematic order. Evaluation of quality control samples injected during each

analytical run indicated that the reported quantitative results may have varied, on average,

up to 26 percent using human plasma calibration curves for all analytes except PFOSA

which may have varied on average up to 43 percent.

Also presented in this report is a calculated total organic fluorine (TOF) index.

TOF was the percent of each of the seven fluorochemicals' molecular weight that was

attributed to organic fluorine [PFOS (64.7%); PFHS (61.9%); PFOA (69.0%); PFOSAA

(55.3%); PFOSA (64.7%); M570 (56.6%) and M556 (58.1%)] multiplied by the ppb

measured for each fluorochemical and then summed across all seven fluorochemicals.

Data Analysis

Measures of central tendency applicable to log normally distributed data (median,

geometric mean) were used for descriptive analyses. In those instances where a sample

was measured below the lower limit of quantitation (LLOQ), the midpoint between zero

and the LLOQ was used for calculation of the geometric mean. An assessment of this

midpoint assumption and how it affected the calculation of the geometric mean was

performed using the 10th and 90th percentile values between zero and the LLOQ for those

values <LLOQ.

In order to minimize parametric assumptions in the estimation of extreme

percentiles of the population, the bootstrap method of Efron (1993) was used to generate

confidence intervals around the empirical percentiles for serum concentrations. In this

method, a large number of replicated estimates of the percentile are generated from full-

size samples of the original observations drawn with replacement. The distribution of the

deviations of replicates from the original-sample estimate mimics the underlying

sampling distribution for the estimate. Bias-corrected, accelerated percentiles were used

to minimize residual bias. The bias correction factor is derived by comparing empirical

percentiles to bootstrap percentiles and acceleration is accomplished by partial

jackknifing.

An analysis of the reliability of the assay was conducted after the original samples

were analyzed. The laboratory was blind to the identity of these samples as they related

to the original values reported. Triplicate samples were analyzed for the highest one

percent of the measured concentrations of PFOS, PFOA and PFHS. If there was

insufficient serum sample left for analysis, the next highest sample was included for

analysis. A 20 percent random sample of the next highest nine percent samples was also

conducted but with only a single measurement. Finally, a five percent sample was

randomly chosen of the remaining 90 percent of all samples. This five percent sample

was also analyzed only once. Altogether, there were 62 samples reanalyzed representing

sera from 44 unique children.

## RESULTS

The results for the reliability analysis for PFOS, PFOA, PFHS, PFOSAA and

M570 using the reanalyzed samples is displayed in Figure 1. There were no measured

concentrations of PFOSA that were above the LLOQs. Only 12 of the 62 M556

concentration comparisons were above the LLOQ; thus, these graphs are not displayed.

There were strong correlations for PFOS (r = .98), PFOA (r = .96) and PFHS (r = .93).

Correlations were slightly less for PFOSAA (r = .69) and for M570 (r = .80). Both

PFOSAA and M570 had many comparisons below the LLOQ as represented in the

graphs near the abscissa (0,0) on the identity (ln y = ln x) line.

Provided in Table 1 is the distribution of the 599 children by age and gender. Altogether there were 299 males and 300 females. Presented in Table 2 is the distribution by states (n = 23) and the District of Columbia. One subject (female) was not analyzed due to an insufficient quantity of serum sample.

The measured concentrations of PFOSA and M556 were predominantly below the LLOQ. For PFOSA, there were no subjects with a concentration above the LLOQ, 457 subjects had concentrations <LLOQ (1.0 ppb), 82 subjects had concentrations <LLOQ (2.0 ppb) and 50 subjects had analyses below the LLOQ but failed to meet the performance standards of the analytical method. As there was only 0.1 ml, on average, per sample, no subsequent analyses were conducted on these 50 samples for PFOSA. For M556, 258 subjects had concentrations that ranged between 2.5 ppb and 9.9 ppb, 263 subjects had concentrations <LLOQ (2.5 ppb) and 77 subjects had concentrations < LLOQ (5.0 ppb). Assuming the midpoint between zero and the LLOQ, the geometric mean for M556 was 2.4 ppb (95% CI 2.2 - 2.5). Because PFOSA and M556 had many analyses <LLOQ, statistical analyses are not presented for these compounds. They were included in the calculation of the TOF index using, for those PFOSA or M556 values <LLOQ, the midpoint between zero and the LLOQ.

The distributions of the five remaining fluorochemicals, PFOS, PFOA, PFHS, PFOSAA and M570, are displayed in Figure 2 for the 598 children samples analyzed. Although the graphs are suggestive of log normal distributions, only the PFOS distribution met such criteria based on the Shapiro-Wilk test. This lack of log normality may be due to the greater proportion of subjects with values <LLOQ for PFOA, PFHS, PFOSAA and M570.

The range, interquartile range, number of samples < LLOQ, cumulative 90th

percentile, median, geometric mean and 95% confidence interval of the geometric mean

for PFOS, PFOA, PFHS, PFOSAA and M570 are provided in Table 3 for all children (N

= 598), males only (N = 300) and females only (N = 298). Overall, the geometric mean

concentration of PFOS was 37.5 ppb (95% CI 36.0-39.1). The PFOS values ranged from

6.7 ppb to 515.0 ppb. Male children had a significantly (p < .01) higher geometric mean

serum PFOS level compared to female children although the absolute difference was not

substantial [male children geometric mean = 40.1 ppb (95% CI 37.7-42.6) vs female

geometric mean = 35.2 ppb (95% CI 33.3-37.2)]. Male children also had significantly

higher geometric mean serum levels of PFOA and PFHS compared to female children.

There were not gender-related geometric mean differences for PFOSAA and M570. The

geometric mean for the calculated TOF index was 38.9 ppb (95% CI 37.2-40.7). The

calculated TOF index range was 9.6 ppb to 803.7 ppb. Geometric means of male

children (41.6 ppb, 95% CI 38.8-44.5) were significantly (p < .01) higher than female

children (36.4 ppb, 95% CI 34.3-38.7).

Measures of central tendency for each of the ages, 2 to 12, are presented in Table

4. Provided in Figure 3 is a graphical distribution (natural log scale) of the five

fluorochemicals by each age stratified by gender. The box covers the interquartile range

of the natural log distribution. The circle within the box is the mean. The whiskers

extend to the last observation within 1.5 times the interquartile range. The dots with lines

through them represent observations outside the 1.5 times interquartile range. Analyzed

as a continuous variable in simple regression models, age was significantly (p < .05)

negatively associated with PFOA and M570 in both males and females but not with

PFOS, PFHS or PFOSAA.

As discussed previously in the Methods, the geometric mean data were calculated

under the assumption that, for individual serum fluorochemical values <LLOQ, the

midpoint between zero and the LLOQ was assigned. For PFOS, no subject had a value

<LLOQ; thus this assumption did not affect its calculation of the geometric mean.

However, many subjects had values less than the LLOQs for PFOA, PFHS, PFOSAA

and M570 (see Table 2). If these values were assumed to be 10% or 90% of this range

between zero and the LLOQ, the respective range of the geometric means (95%

confidence interval in parenthesis) became: PFOA 4.6 ppb (4.3-4.9) to 5.0 ppb (4.8-5.2);

PFHS 3.2 ppb (2.8-3.8) to 5.2 ppb (4.7-5.7); PFOSAA 2.5 ppb (2.2-2.7) to 3.7 ppb (3.6-

3.9) and M570 1.1 ppb (1.0-1.3) to 2.3 ppb (2.2-2.5). These geometric mean values were

not substantially different than those calculated using the midpoint between zero and the

<LLOQ as presented in Table 2. Consequently, the midpoint between zero and the

LLOQ was used for the analyses.

Provided in Figure 4 is a graphical presentation of the fluorochemical data

(natural log scale) by the 23 states and the District of Columbia stratified by gender.

Interpretation of the graphs is comparable to those discussed above for Figure 3. For

PFOS, mean values were comparable for the various locations. Statistical analyses by

state were problematic because of the limited sample size for any given age and gender

combination.

Scatter plots (log scale) between the five fluorochemicals are displayed in Figure

5. PFOS and PFOA were highly correlated (r = .70). PFOS had a lower correlation with

PFOSAA (r = .43) and M570 (r = .42). The correlation between PFOSAA and M570 was

less (r = .27). The remaining scatter plots display the correlations between PFOS and

PFHS (r = 0.66) and PFOA and PFHS (r = 0.48). Both PFOSAA and M570, adjusted for

age, gender and their interaction, were significant predictors of PFOS in a multivariable

model (Table 5). Almost seventy percent of the variation of PFOS, however, was left

unexplained. Adjusted for age, gender and their interaction, PFOA remained a

significant predictor of PFOS (Table 6). A quadratic term was significant in the model

which examined the association between PFOS and PFHS adjusted for age, gender and

their interactions (Table 7).

Presented in Table 8 are the results from bootstrap analyses conducted to provide

tolerance limits. The tolerance limits represent the limit of each fluorochemical within

which the stated proportion of the population is expected to be found. Presented are the

mean values of the five serum fluorochemicals and TOF for the 90th, 95th and 99th percent

tolerance limits along with the upper limit (bound) from the 95% confidence interval.

For example, the mean of the 95% tolerance limit for PFOS was 88.5 ppb with an upper

95% percent confidence limit of 97.0 ppb. At the lowest tolerance limit analyzed, (90%),

the mean for PFOS was 70.6 ppb with an upper 95% confidence limit of 75.2 ppb. At the

highest tolerance limit analyzed, the (99%), the mean was 140.6 ppb with an upper 95

percent confidence limit of 217.0 ppb. For other fluorochemicals analyzed, the mean of

the 95% tolerance limit for PFOA was 10.1 ppb with an upper 95% confidence limit of

11.0 ppb. For PFHS, the mean of the 95% tolerance limit was 64.5 ppb with an upper

95% confidence limit of 80.6 ppb. The mean of the 95% tolerance limit for PFOSAA

was 10.4 ppb with an upper 95% confidence limit of 11.2 ppb. For M570, the mean was

11.9 ppb for a 95% tolerance limit with an upper 95% confidence limit of 14.8 ppb.

Finally, for the calculated index of TOF, the mean was 112.1 ppb for the 95% tolerance

limit with an upper 95% confidence limit of 125.0 ppb.


DISCUSSION

As seen in Figure 6, the geometric mean measured concentrations for these

pediatric samples is consistent with those reported for adult blood donors (Olsen et al

2000a) and elderly participants of a longitudinal study of cognitive function (Olsen et al

2002b). No substantial differences were observed for PFOS or PFOA between the three

study populations. Interpretation of the PFHS, PFOSAA and M570 is more problematic

because the LLOQs varied slightly between studies and thus the assumption of a

midpoint value may unduly influence a geometric mean calculation when comparing

mean measured concentrations for the three studies.

Displayed in Figure 7 is another perspective regarding the differences in

measured fluorochemical concentration distributions between the pediatric, adult and

elderly population data. It is clearly evident that the 95% tolerance limits for PFHS and,

to a lesser extent M570, were substantially different in children than compared to the

adult and the elderly populations whereas the mean concentrations of the 95% tolerance

limits were similar for PFOS, PFOA and PFOSAA. These findings suggest a different

exposure pattern for some children compared to the adult and the elderly populations.

While residual PFHS related chemistry may have existed in POSF related materials, it

was an intentional major ingredient only in fire fighting foam and an after market carpet

protector, which was discontinued in 1999. One potential hypothesis to explain the

difference between adult and children sera PFHS levels could be the differential exposure to carpet known to exist between these two population groups. The mean 95 percent tolerance limit for M570 was also greater in children than in the adults and the elderly. M570 can be a residual analyte of N-methyl perfluorooctanesulfonamidoacetate surface protectants which would include carpet and textile applications. An alternative hypothesis, which we suspect is much less likely, is that a segment of the pediatric population clears PFHS and M570 differently than adults or the elderly. There appeared to be similar comparisons between the three populations for the mean 95% tolerance limit for PFOSAA which may be a residual analyte associated with the N-EtFOSE paper and packaging protectant products.

Previous measurements of human serum samples obtained in the United States have been comparable to what has been reported in the children, adult and elderly studies. The mean PFOS serum level was 30 ppb in 18 pooled blood banks, 44 ppb from a pooled commercial sample of 500 donors, 33 ppb from a different pooled commercial sample of 200 donors and 28 ppb in 65 commercial individual human sera samples (3M Company 2000; Hansen et al 2001). These findings were also comparable to a limited number of European samples which found mean serum PFOS concentrations at 17 ppb in 5 pooled samples from a Belgium blood bank, 53 ppb in 6 pooled samples from the Netherlands, 37 ppb from 6 pooled blood samples from Germany and ranged between <LLOQ (3.2 ppb) to 85 ppb in 39 individual Swedes (3M Company, 2000). The mean calculated TOF index used in the present study was also consistent with the low ppb total organic fluorine measurements of general population samples that have been reported since the 1960's (Taves 1968; Taves et al 1976; Singer and Ophaug 1979; Belisle 1981).

As was also observed in the adult and elderly studies (Olsen et al 2002a; 2002b), we found a strong correlation between PFOS and PFOA in the children sera. Whereas PFOS has been routinely measured in human populations, wildlife, marine mammals and piscivorous birds (Giesy and Kannan 2001; Kannan et al 2001a; 2001b; Hansen et al 2001; 3M Company 2000), serum PFOA concentrations, to date, have been consistently quantified (i.e., measured above the LLOQs) primarily in humans. This association is of significant interest because PFOA cannot convert to PFOS (or vice versa). Whether this association is due to the presence of PFOA as a by-product in POSF-related production or to other non-related environmental exposures or consumer products from other manufacturers (e.g., higher chain telomers) remains to be answered. Another unanswered question is whether perfluoroctanesulfonamides can metabolize in humans to PFOA. Any of these explanations coupled with the suspected long serum half-lives in humans for PFOS (8.7 years (SD = 6.1)) and PFOA (4.4 years (SD = 3.5)) as reported by Burris et al (2002) could explain the strong correlation between PFOS and PFOA. It should also be noted that the serum PFHS half-life reported by Burris et al (2002) was uninterpretable (-2.27 years, SD = 23.1) but possibly indicative of a long (years) serum half-life.

PFOS was also correlated with two fluorochemicals, PFOSAA and M570, known to be analytes from exposure to consumer products involving paper/packaging and carpet/textile protectants, respectively. Overall, the data, to date, indicate that PFOS bioaccumulation in animals may be primarily through environmental sources whereas both environmental and consumer product exposures likely contribute to serum PFOS concentrations in humans.

As with any interpretation of data obtained from a study population, questions arise regarding its representativeness and the ability to generalize from the data collected. We are confident that our sampling procedures allowed for an adequate representation of the original study database. We believe this population of children is not unique due to the high prevalence of group A streptococcal infections in children. The only other information available for analysis were the age, gender and residence (state) of the children. We are unaware of any database that can be considered generalizable to the diverse United States pediatric general population without measures of random and systematic bias incorporated in the data analysis.

Given the consistency of the data analyzed, to date, we hypothesize that the average serum PFOS concentrations in non-occupational adult populations likely ranges between 30 to 40 ppb with 95% of a population's serum PFOS below 100 ppb. Understanding these serum PFOS levels in human populations will be useful in risk characterization since serum PFOS likely reflects cumulative human exposure (3M Company 2000). Currently available data (unpublished reports to U.S. EPA:Docket No. FYI-0500-01378) suggest, to date, that the serum concentrations observed in humans are substantially less than those required to cause adverse effects in laboratory animals (3M Company 2000). The data in the present study regarding the higher mean 95% tolerance limits for PFHS and M570, compared to those found in the adults and the elderly, suggest that some children may have had a greater exposure experience to products containing PHSF and N-MeFOSE surface protectants.

## ACKNOWLEDGEMENTS

# REFERENCES

3M Company (2000). SIDS Initial Assessment Report Perfluorooctane Sulfonic Acid and its Salts. St. Paul:3M Company, September 20, 2000.

Belisle J (1981). Organic fluorine in human serum: natural versus industrial sources. Science 212:1509-1510.

Burris JM, Lundberg JK, Olsen GW, Simpson C, Mandel JH (2002). Interim Report: Determination of serum half-lives of several fluorochemicals. St. Paul:3M Company, January 11, 2002.

Efron B, Tibshiarani RJ. An Introduction to the Bootstrap. In: Cox DR, Hinkley DV, Reid N, Rubin DB, Silverman BW, eds. Monographs on Statistics and Applied Probability. Vol 57 New York:Chapman H Hall.

Giesy JP, Kannan K (2001). Global distribution of perfluorooctane sulfonate in wildlife. Environ Sci Technol 35(7):1339-1342.

Hansen KJ, Clemen LA, Ellefson ME, Johnson HO (2001a). Compound-specific quantitative characterization of organic fluorochemicals in biological matrices. Environ Sci Technol 35:766-770.

Kannan K, Koistenen J, Beckmen K, Evans T, Gorzelany JF, Hansen KJ, Jones PD, Helle E. Nyman M, Giesy JP (2001b). Accumulation of perfluorooctane sulfonate in marine mammals. Environ Sci Technol 35(8):1593-1598.

Kannan K, Franson JC, Bowerman WW, Hansen KJ, Jones PD, Giesy JP (2001). Perfluorooctane Sulfonate in fish-eating water birds including bald eagles and albatrosses. Environ Sci Technol·35(15):3065-3070.

Kaplan EL, Rothermel CD, Johnson DR (1998). Antistreptolysin O and anti-deoxyribonuclease B titers: normal values for children ages 2 to 12 in the United States. Pediatrics 101:86-88.

Leibrecht BC, Hogan JM, Luz GA, Tobias KI (1976). Donor and nondonor motivations. Transfusion 16:182-189.

Natrella MG (1966). Experimental Statistics. NewYork:Wile & Sons, pp 15.

Northwest Bioanalytical (NWB, 2002). Quantitative determination of PFOS and related compounds in human serum by LC/MS/MS. November 30, 2001.

Olsen GW, Burris JM, Mandel JH, Zobel LR (1999). Serum perfluorooctane sulfonate and hepatic and lipid clinical chemistry tests in fluorochemical production employees. JOEM 41:799-806.

Olsen GW, Burris JM, Lundberg JK, Hansen KJ, Mandel JH, Zobel LR (2002a). Identification of fluorochemicals in human sera. I. American Red Cross blood donors. St. Paul:3M Company (unpublished report).

Olsen GW, Burris JM, Lundberg JK, Hansen KJ, Mandel JH, Zobel LR (2002b). Identification of fluorochemicals in human sera. II. Elderly Participants of the Adult Changes in Thought Study, Seattle, Washington St. Paul:3M Company (unpublished report).

Singer L, Phaug RH (1979). Concentrations of ionic, total, and bound fluoride in plasma. Clin Chem 25:523-525.

Taves D (1968). Evidence that there are two forms of fluoride in human serum. Nature 217:1050-1051.

Taves D, Guy W, Brey W (1976). Organic fluorocarbons in human plasma: Prevalence and characterization. In: Filler R, eds. Biochemistry Involving Carbon-Fluorine Bonds. Washington DC:American Chemical Society, pp 117-134.

Table 1
Distribution of All Children (N = 599) by Age and Gender

| Age | Male | Female | Total |
|---|---|---|---|
| 2 | 18 | 9 | 27 |
| 3 | 25 | 26 | 51 |
| 4 | 36 | 45 | 81 |
| 5 | 40 | 40 | 80 |
| 6 | 40 | 40 | 80 |
| 7 | 30 | 30 | 60 |
| 8 | 30 | 30 | 60 |
| 9 | 20 | 20 | 40 |
| 10 | 20 | 20 | 40 |
| 11 | 20 | 20 | 40 |
| 12 | 20 | 20 | 40 |
| TOTAL | 299 | 300 | 599 |

Table 2
Distribution of Children (N = 599) by Location, Gender and Mean Age

| State | Males | Females | Total | Mean Age |
|-------|-------|---------|-------|----------|
| Alabama | 10 | 12 | 22 | 8.3 |
| Arizona | 7 | 11 | 18 | 6.8 |
| California | 25 | 22 | 47 | 6.0 |
| Colorado | 22 | 17 | 39 | 6.6 |
| District of Columbia | 17 | 11 | 28 | 6.1 |
| Florida | 16 | 26 | 42 | 6.4 |
| Idaho | 10 | 6 | 16 | 8.1 |
| Illinois | 1 | 1 | 2 | 5.0 |
| Kansas | 10 | 3 | 13 | 6.4 |
| Kentucky | 11 | 7 | 18 | 6.9 |
| Massachusetts | 24 | 21 | 45 | 6.3 |
| Michigan | 5 | 4 | 9 | 8.3 |
| Missouri | 4 | 6 | 10 | 7.8 |
| North Carolina | 15 | 18 | 33 | 6.7 |
| Nebraska | 2 | 3 | 5 | 6.8 |
| New Jersey | 23 | 15 | 38 | 6.9 |
| New Mexico | 14 | 14 | 28 | 7.6 |
| New York | 17 | 13 | 30 | 6.3 |
| Ohio | 16 | 17 | 33 | 6.3 |
| Oklahoma | 10 | 18 | 28 | 6.3 |
| Pennsylvania | 6 | 3 | 9 | 5.9 |
| Texas | 20 | 27 | 47 | 6.0 |
| Utah | 10 | 16 | 26 | 6.8 |
| Virginia | 4 | 19 | 23 | 8.3 |
| TOTAL | 299 | 300 | 599 | 6.7 |

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Table 3

Measures of Central Tendency of Serum Fluorochemicals for All Children (N = 598) and by Gender

| | PFOS | PFOA | PFHIS | PFOSAA | M570 |
|---|---|---|---|---|---|
| **All Children (N = 598)** | | | | | |
| Range | 6.7 – 515.0 | <LOQ (1.9) – 56.1 | <LOQ (1.4) – 711.7 | <LOQ (1.6) – 23.8 | <LOQ (1.0) – 48.0 |
| Q1 – Q3 | 27.6 – 51.0 | 3.8 – 6.7 | 1.6 – 10.8 | 2.1 – 5.6 | <LOQ (1.0) – 3.8 |
| <LOQ (N) | - | < 1.9 (5) | < 1.4 (92) | < 1.6 (67) | < 1.0 (140) |
| | | < 2.9 (20) | < 2.4 (37) | < 2.6 (47) | < 2.0 (60) |
| Cumulative 90% | 70.8 | 8.5 | 35.3 | 8.8 | 7.3 |
| Median | 36.7 | 5.1 | 3.8 | 3.7 | 1.8 |
| Geometric Mean | 37.5 | 4.9 | 4.5 | 3.3 | 1.9 |
| 95% C.I. Geometric Mean | 36.0 – 39.1 | 4.7 – 5.1 | 4.1 – 5.1 | 3.1 – 3.6 | 1.7 – 2.1 |
| **Male Children (N = 300)** | | | | | |
| Range | 11.4 – 515.0 | <LOQ (2.9) – 56.1 | <LOQ (1.4) – 711.7 | <LOQ (1.6) – 20.7 | <LOQ (1.0) – 48.0 |
| Q1 – Q3 | 28.7 – 53.9 | 3.9 – 6.9 | 1.9 – 12.2 | 2.0 – 5.8 | <LOQ (1.0) – 4.2 |
| <LOQ (N) | - | < 2.9 (11) | < 1.4 (34) | < 1.6 (40) | < 1.0 (66) |
| | | | < 2.4 (20) | < 2.6 (22) | < 2.0 (31) |
| Cumulative 90% | 75.6 | 9.0 | 38.5 | 8.8 | 7.5 |
| Median | 39.4 | 5.2 | 4.4 | 3.7 | 2.0 |
| Geometric Mean | 40.1 | 5.2 | 5.3 | 3.3 | 2.0 |
| 95% C.I. Geometric Mean | 37.7 – 42.6 | 4.9 – 5.2 | 4.5 – 6.3 | 3.0 – 3.6 | 1.8 – 2.1 |

**Female Children**
**(N = 298)**

| | | | | | |
|---|---|---|---|---|---|
| Range | 6.7 – 165.0 | <LOQ (1.9) – 18.6 | <LOQ (1.4) – 170.0 | <LOQ (1.6) – 23.8 | <LOQ (1.0) – 38.1 |
| Q1 – Q3 | 27.0 – 46.3 | 3.5 – 6.3 | <LOQ (2.4) – 10.2 | 2.2 – 5.6 | <LOQ (1.0)– 3.7 |
| <LOQ (N) | - | <1.9 (5) | <1.4 (58) | <1.6 (27) | <1.0 (74) |
| | | <2.9 (9) | <2.4 (17) | <2.6 (25) | <2.0 (29) |
| Cumulative 90% | 64.8 | 8.0 | 22.5 | 8.7 | 6.9 |
| Median | 34.7 | 4.9 | 3.3 | 3.8 | 1.7 |
| Geometric Mean | 35.2 | 4.7 | 3.9 | 3.4 | 1.8 |
| 95% C.I. Geometric Mean | 33.3 – 37.2 | 4.4 – 4.9 | 3.3 – 4.5 | 3.1 – 3.7 | 1.6 – 2.0 |

Table 4. Measures of Central Tendency of Serum Fluorochemicals for All Children (N = 598) by Age

| Age | PFOS | PFOA | PFHS | PFOSAA | M570 |
|---|---|---|---|---|---|
| **Age 2** | | | | | |
| Range | 8.8 – 217.0 | <LOQ (1.9) – 34.2 | <LOQ (1.4) – 497.0 | <LOQ (1.6) – 10.5 | <LOQ (1.0) – 16.3 |
| Q1 – Q3 | 16.8 – 41.4 | 2.5 – 6.2 | <LOQ (1.4) – 17.1 | 1.7 – 5.7 | <LOQ (2.0) – 5.1 |
| Cumulative 90% | 88.2 | 17.7 | 74.5 | 9.5 | 10.0 |
| Median | 27.1 | 4.1 | 3.6 | 3.4 | 2.5 |
| Geometric Mean | 28.6 | 4.5 | 4.1 | 3.3 | 2.5 |
| 95% C.I. Geometric Mean | 21.4 – 38.1 | 3.3 – 6.3 | 2.0 – 8.5 | 2.4 – 4.5 | 1.6 – 3.5 |
| **Age 3** | | | | | |
| Range | 6.7 – 184.0 | <LOQ (1.9) – 16.1 | <LOQ (1.4) – 170.0 | <LOQ (1.6) – 15.8 | <LOQ (1.0) – 34.4 |
| Q1 – Q3 | 24.3 – 50.6 | 4.2 – 6.7 | <LOQ (2.4) – 12.2 | 2.1 – 5.4 | <LOQ (2.0) – 3.9 |
| Cumulative 90% | 104.1 | 9.8 | 89.0 | 7.0 | 9.0 |
| Median | 30.3 | 5.4 | 3.9 | 3.7 | 2.0 |
| Geometric Mean | 34.9 | 5.1 | 4.8 | 3.1 | 2.1 |
| 95% C.I. Geometric Mean | 29.0 – 41.8 | 4.4 – 5.9 | 3.0 – 7.5 | 2.5 – 3.8 | 1.6 – 2.8 |

Age 4

| | | | | | |
|---|---|---|---|---|---|
| Range | 11.6 – 325.0 | 2.0 – 56.1 | <LOQ 1.4) – 416.0 | <LOQ (1.6) – 23.8 | <LOQ (1.0) – 48.0 |
| Q1 – Q3 | 27.6 – 43.1 | 4.2 – 7.2 | 1.9 – 9.2 | 2.0 – 6.0 | <LOQ (2.0) – 4.6 |
| Cumulative 90% | 60.5 | 10.1 | 28.3 | 7.8 | 8.0 |
| Median | 34.0 | 5.5 | 3.5 | 3.9 | 2.2 |
| Geometric Mean | 35.3 | 5.7 | 4.5 | 3.4 | 2.2 |
| 95% C.I. Geometric Mean | 31.8 – 39.2 | 5.1 – 6.4 | 3.4 – 6.0 | 2.9 – 4.0 | 1.7 – 2.8 |

Age 5

| | | | | | |
|---|---|---|---|---|---|
| Range | 15.8 – 96.5 | <LOQ (2.9) – 11.5 | <LOQ (1.4) – 80.6 | <LOQ (1.6) – 19.6 | <LOQ (1.0) – 38.1 |
| Q1 – Q3 | 30.3 – 56.4 | 4.3 – 7.1 | 1.8 – 11.0 | 2.3 – 6.6 | <LOQ (2.0) – 4.7 |
| Cumulative 90% | 73.1 | 9.0 | 27.8 | 10.3 | 10.7 |
| Median | 39.7 | 5.5 | 4.1 | 4.7 | 2.3 |
| Geometric Mean | 40.5 | 5.4 | 4.4 | 4.0 | 2.3 |
| 95% C.I. Geometric Mean | 36.8 – 44.5 | 4.9 – 5.9 | 3.3 – 5.8 | 3.3 – 4.7 | 1.8 – 3.0 |

## Age 6

| | | | | | |
|---|---|---|---|---|---|
| Range | 12.2 – 515.0 | <LOQ (2.9) – 20.2 | <LOQ (1.4) – 711.7 | <LOQ (1.6) – 12.9 | <LOQ (1.0) – 23.0 |
| Q1 – Q3 | 30.0 – 56.3 | 4.2 – 6.9 | 2.3 – 10.5 | 2.2 – 6.2 | <LOQ (1.0) – 4.9 |
| Cumulative 90% | 76.4 | 8.6 | 27.3 | 9.4 | 13.5 |
| Median | 40.0 | 5.3 | 4.3 | 4.0 | 2.0 |
| Geometric Mean | 41.0 | 5.3 | 5.1 | 3.5 | 2.1 |
| 95% C.I. Geometric Mean | 36.2 – 46.5 | 4.8 – 5.9 | 3.8 – 6.8 | 3.0 – 4.2 | 1.6 – 2.8 |

## Age 7

| | | | | | |
|---|---|---|---|---|---|
| Range | 16.7 – 134.0 | <LOQ (2.9) – 11.0 | <LOQ (1.4) – 94.2 | <LOQ (1.6) – 9.6 | <LOQ (1.0) – 17.1 |
| Q1 – Q3 | 27.3 – 49.7 | 3.5 – 6.1 | 2.6 – 19.5 | 1.8 – 4.4 | 0.6 – 3.3 |
| Cumulative 90% | 74.2 | 7.7 | 51.0 | 6.0 | 6.6 |
| Median | 36.7 | 4.6 | 6.6 | 2.8 | 1.8 |
| Geometric Mean | 38.4 | 4.6 | 7.3 | 2.7 | 1.7 |
| 95% C.I. Geometric Mean | 34.3 – 43.0 | 4.1 – 5.1 | 5.2 – 10.3 | 2.3 – 3.2 | 1.3 – 2.2 |

### Age 8

| | | | | | |
|---|---|---|---|---|---|
| Range | 17.2 – 116.0 | 2.1 – 16.4 | <LOQ (1.4) – 180.0 | <LOQ (1.6) – 21.7 | <LOQ (1.0) – 17.8 |
| Q1 – Q3 | 32.5 – 55.3 | 4.1 – 7.2 | 1.6 – 9.4 | 2.6 – 6.7 | <LOQ (2.0) – 4.0 |
| Cumulative 90% | 78.1 | 8.9 | 50.5 | 11.5 | 7.0 |
| Median | 38.1 | 5.2 | 4.3 | 3.8 | 1.7 |
| Geometric Mean | 41.8 | 5.4 | 4.7 | 3.9 | 1.9 |
| 95% C.I. Geometric Mean | 37.3 – 46.8 | 4.9 – 6.0 | 3.3 – 6.9 | 3.1 – 4.7 | 1.5 – 2.5 |

### Age 9

| | | | | | |
|---|---|---|---|---|---|
| Range | 17.5 – 122.0 | <LOQ (2.9) – 11.6 | <LOQ (1.4) – 145.0 | <LOQ (1.6) – 11.6 | <LOQ (1.0) – 6.4 |
| Q1 – Q3 | 34.1 – 54.7 | 3.8 – 6.3 | 2.2 – 13.6 | <LOQ (2.6) – 5.2 | <LOQ (2.0) – 3.0 |
| Cumulative 90% | 67.2 | 7.0 | 36.8 | 8.9 | 4.3 |
| Median | 44.1 | 5.3 | 4.7 | 3.1 | 1.5 |
| Geometric Mean | 42.8 | 4.9 | 5.6 | 2.7 | 1.5 |
| 95% C.I. Geometric Mean | 37.6 – 48.7 | 4.3 – 5.6 | 3.6 – 8.6 | 2.1 – 3.5 | 1.2 – 2.0 |

## Age 10

| Range | 10.2 – 98.9 | <LOQ (2.9) – 8.9 | <LOQ (1.4) – 88.7 | <LOQ (1.6) – 20.7 | <LOQ (1.0) – 7.0 |
|---|---|---|---|---|---|
| Q1 – Q3 | 29.1 – 50.2 | 3.6 – 6.2 | 1.2 – 7.9 | 2.1 – 5.1 | <LOQ (2.0) – 3.8 |
| Cumulative 90% | 70.1 | 7.2 | 35.3 | 8.7 | 5.7 |
| Median | 33.9 | 4.7 | 2.5 | 3.6 | 1.9 |
| Geometric Mean | 37.7 | 4.6 | 3.2 | 3.2 | 1.8 |
| 95% C.I. Geometric Mean | 32.5 – 43.7 | 4.1 – 5.2 | 2.0 – 4.9 | 2.5 – 4.1 | 1.4 – 2.4 |

## Age 11

| Range | 10.4 – 106.0 | <LOQ (1.9) – 9.0 | <LOQ (1.4) – 75.4 | <LOQ (1.6) – 18.7 | <LOQ (1.0) – 11.3 |
|---|---|---|---|---|---|
| Q1 – Q3 | 25.4 – 48.9 | 2.6 – 5.4 | <LOQ (1.4) – 6.6 | <LOQ (2.6) – 6.8 | <LOQ (1.0) – 2.5 |
| Cumulative 90% | 68.7 | 7.0 | 37.0 | 14.7 | 5.0 |
| Median | 35.8 | 3.8 | 1.8 | 4.2 | <LOQ (2.0) |
| Geometric Mean | 33.5 | 3.6 | 2.7 | 3.7 | 1.2 |
| 95% C.I. Geometric Mean | 28.2 – 39.7 | 3.0 – 4.3 | 1.7 – 4.3 | 2.7 – 5.0 | 0.9 – 1.6 |

## Age 12

| | | | | | |
|---|---|---|---|---|---|
| Range | 11.4 – 124.0 | <LOQ (1.9) – 14.6 | <LOQ (1.4) – 35.7 | <LOQ (1.6) – 11.3 | <LOQ (1.0) – 31.0 |
| Q1 – Q3 | 22.7 – 43.3 | 2.6 – 4.9 | 0.8 – 10.1 | 1.5 – 5.3 | <LOQ (1.0) – 2.6 |
| Cumulative 90% | 65.9 | 5.8 | 21.2 | 7.7 | 4.7 |
| Median | 34.0 | 3.8 | 3.9 | 3.7 | 1.3 |
| Geometric Mean | 32.8 | 3.5 | 3.5 | 3.0 | 1.4 |
| 95% C.I. Geometric Mean | 27.9 – 38.5 | 3.0 – 4.2 | 2.3 – 5.4 | 2.4 – 3.9 | 1.0 – 1.8 |

Table 5
Multivariable Regression Model of PFOS[*] by
PFOSAA[*], M570[*], Age, Gender and Their Interaction

|  | Coefficient | SE | t ratio | p value |
|---|---|---|---|---|
| Intercept | 3.1 | 0.05 | 58.1 | < .0001 |
| PFOSAA[*] | 0.2 | 0.02 | 9.7 | < .0001 |
| M570[*] | 0.2 | 0.02 | 9.3 | < .0001 |
| Age | 0.02 | 0.006 | 2.5 | .01 |
| Gender | - 0.04 | 0.05 | -0.8 | .40 |
| Age x Gender | - 0.003 | 0.006 | -0.6 | .58 |

N = 598

[*]Natural log

Adjusted $r^2$ = .31

Gender: females = 1; males = 0

t ratio = coefficient/SE (standard error)

Table 6
Multivariable Regression Model of PFOS[*] by
PFOA[*], Age, Gender and Their Interaction

|  | Coefficient | SE | t ratio | p value |
|---|---|---|---|---|
| Intercept | 2.2 | 0.07 | 33.5 | < .0001 |
| PFOA[*] | 0.8 | 0.03 | 25.4 | < .0001 |
| Age | 0.03 | 0.005 | 6.1 | < .0001 |
| Gender | 0.0008 | 0.04 | 0.02 | .98 |
| Age x Gender | - 0.004 | 0.005 | -0.8 | .41 |

N = 598

[*]Natural log

Adjusted $r^2$ = .53

Gender: females = 1; males = 0

t ratio = coefficient/SE (standard error)

Table 7
Multivariable Regression Model of PFOS[*] by
PFHS[*], Age, Gender and Their Interaction

|  | Coefficient | SE | t ratio | p value |
|---|---|---|---|---|
| Intercept | 3.2 | 0.04 | 72.4 | < .0001 |
| PFHS[*] | 0.1 | 0.03 | 4.6 | < .0001 |
| [PFHS]$^2$ [*] | 0.03 | 0.006 | 5.1 | < .0001 |
| Age | 0.01 | 0.005 | 2.2 | .03 |
| Gender | 0.03 | 0.04 | 0.7 | .47 |
| Age x Gender | - 0.008 | 0.005 | 1.6 | .12 |

N = 598

[*]Natural log

Adjusted $r^2$ = .47

Gender: females = 1; males = 0

t ratio = coefficient/SE (standard error)

Table 8
Tolerance Limits and Their Associated Means and Upper 95th Percent
Confidence Limits for Serum Fluorochemicals and Calculated
Total Organic Fluorine Index

| | Tolerance Limit | Mean | Upper 95th Percent Confidence Limit |
|---|---|---|---|
| PFOS | 90% | 70.6 | 75.2 |
| | 95% | 88.5 | 97.0 |
| | 99% | 140.6 | 217.0 |
| PFOA | 90% | 8.4 | 9.0 |
| | 95% | 10.1 | 11.0 |
| | 99% | 16.6 | 20.2 |
| PFHS | 90% | 33.9 | 38.7 |
| | 95% | 64.5 | 80.6 |
| | 99% | 156.3 | 416.0 |
| PFOSAA | 90% | 8.6 | 9.1 |
| | 95% | 10.4 | 11.2 |
| | 99% | 17.8 | 20.7 |
| M570 | 90% | 7.2 | 8.2 |
| | 95% | 11.9 | 14.8 |
| | 99% | 25.7 | 38.1 |
| TOF | 90% | 77.8 | 91.5 |
| | 95% | 112.2 | 125.0 |
| | 99% | 203.0 | 482.1 |

Figure 1. Analysis of Split Samples for Reliability Assessment for PFOS, PFOA, PFHS, PFOSAA and M570
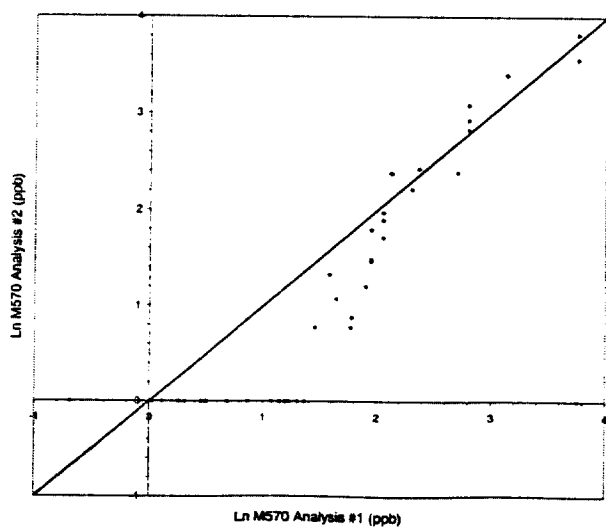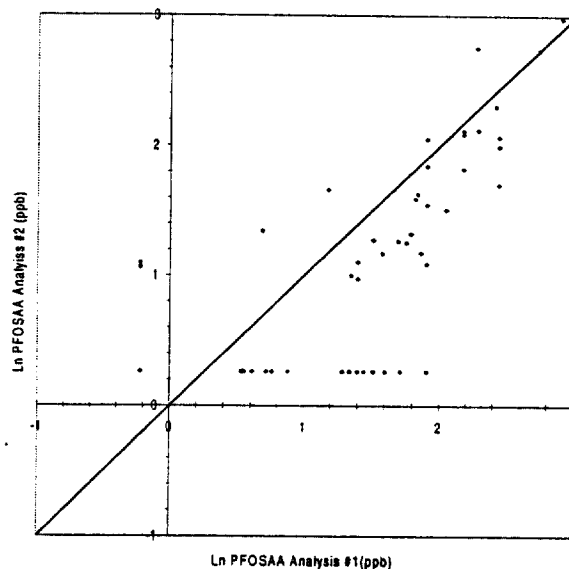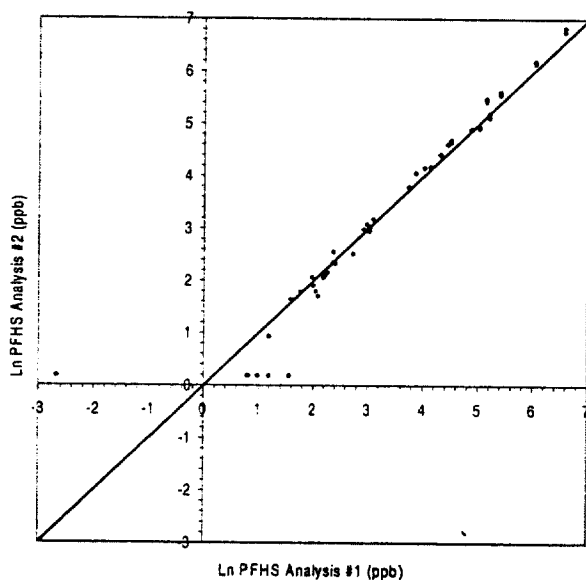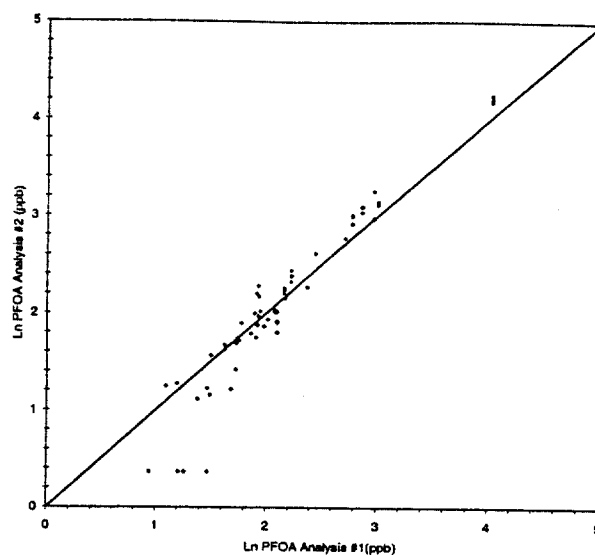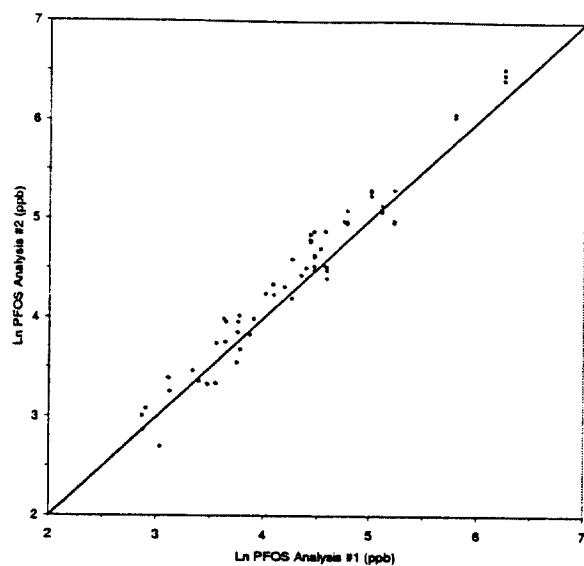
Figure 2. Pediatric Study Population Distribution of Measured Fluorochemical Concentrations
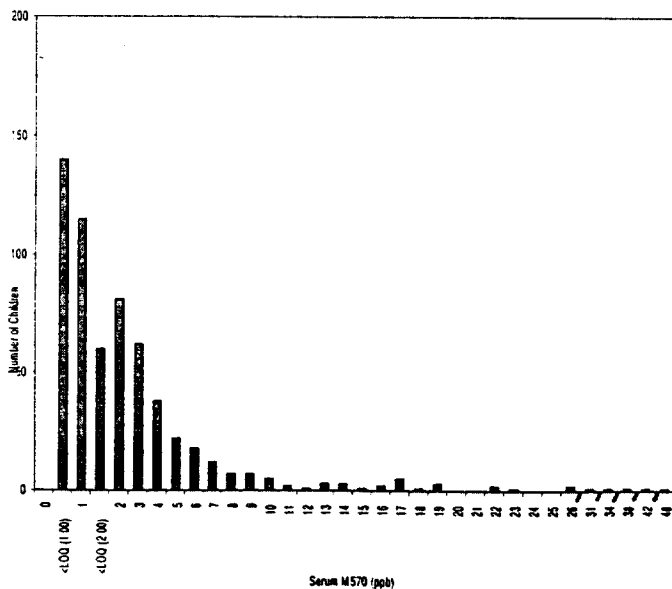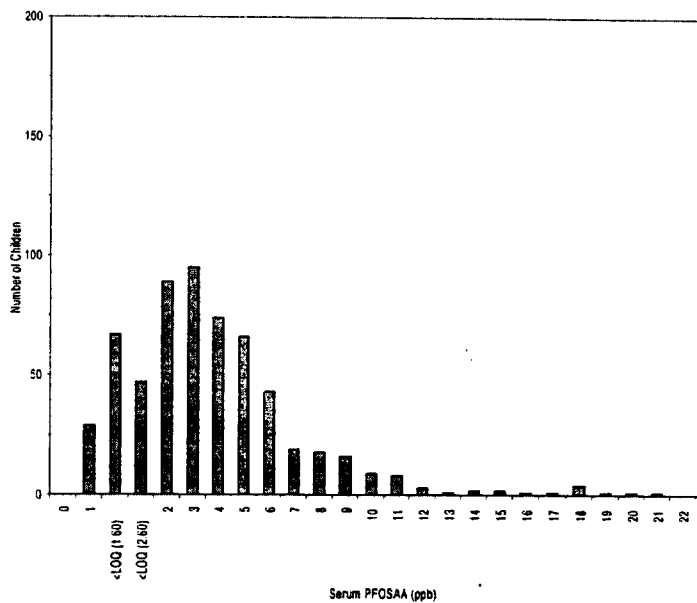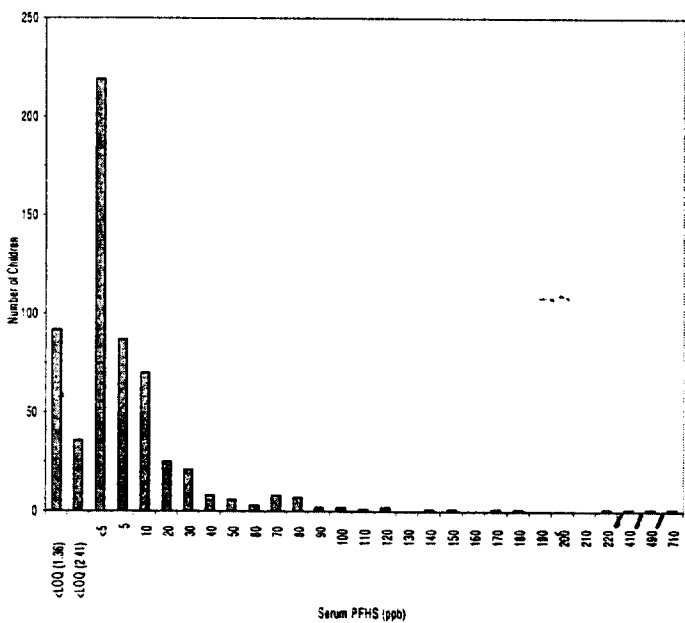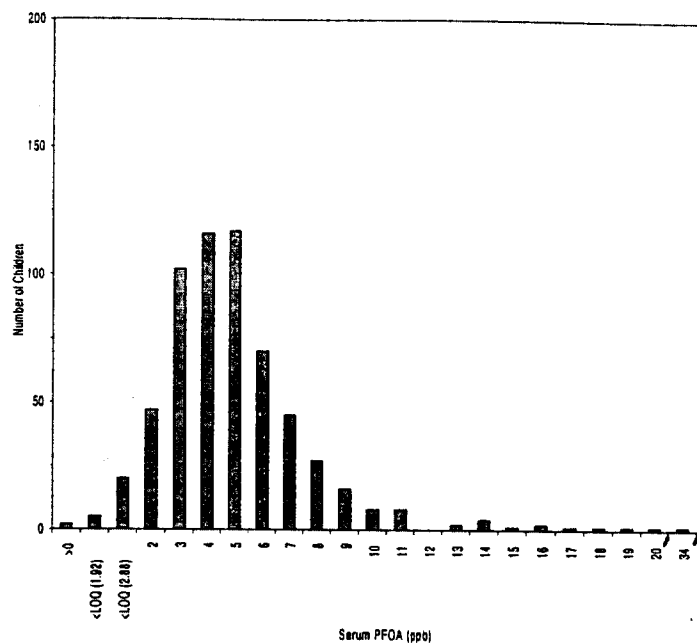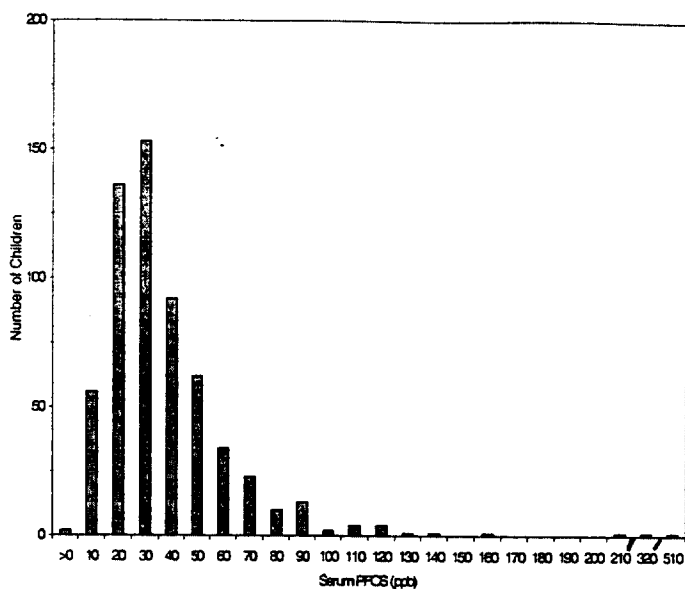
Figure 3. Box and Whisker Plots of Serum Fluorochemical Concentrations by Age and Gender
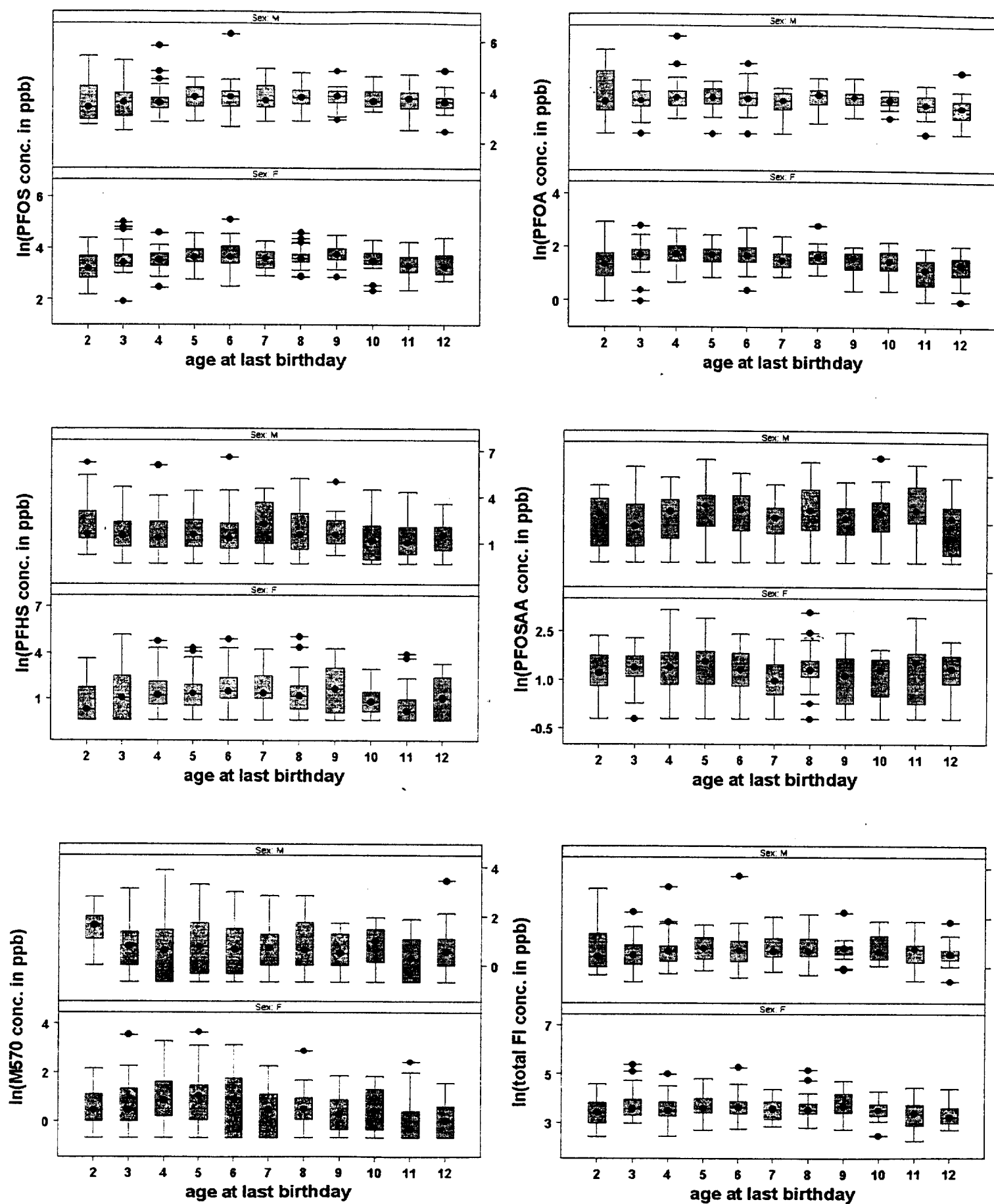
# Figure 4. Box and Whisker Plots of Serum Fluorochemical Concentrations by Gender and State
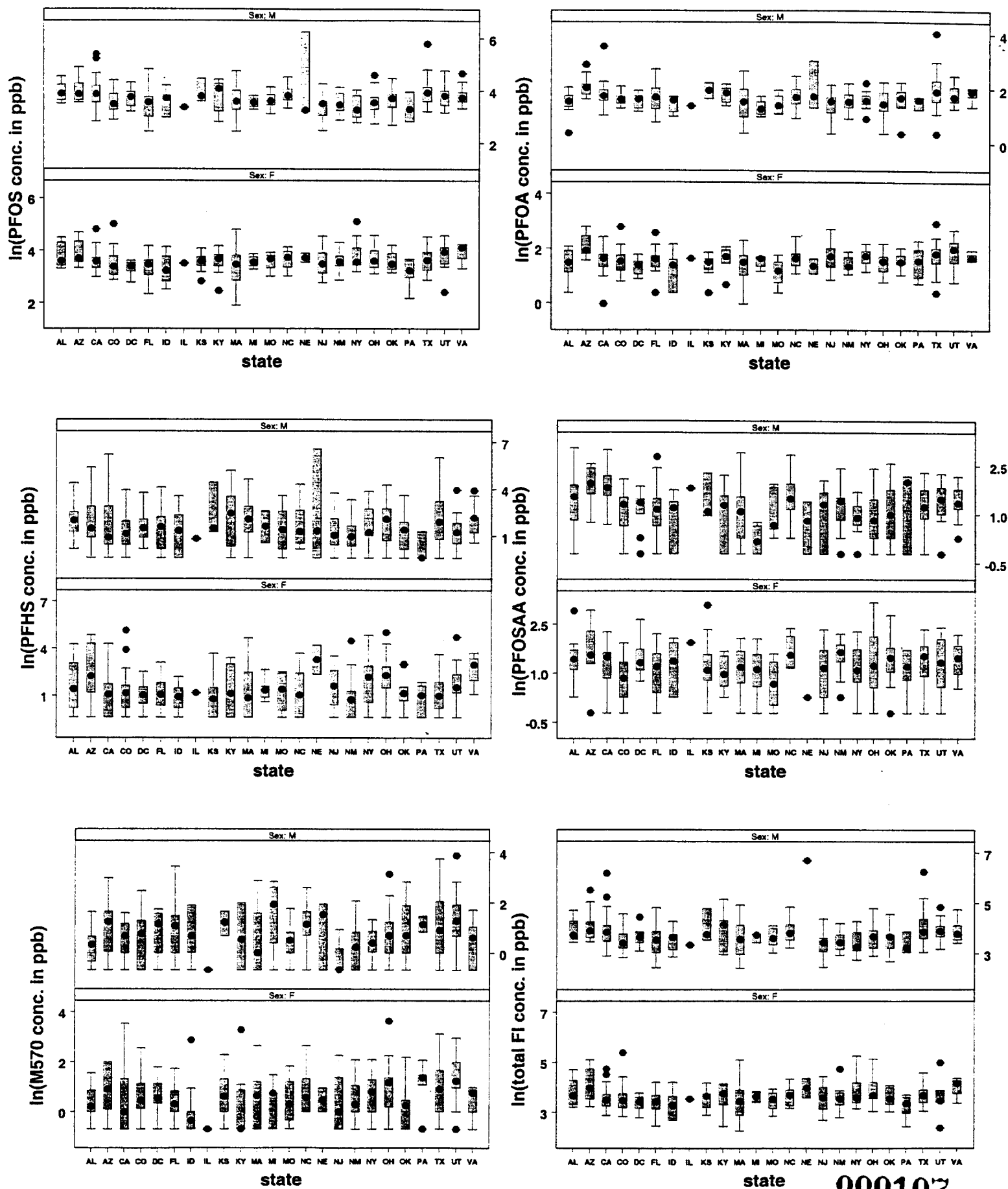
Figure 5. Scatter Plots (log scale) of Fluorochemical Associations
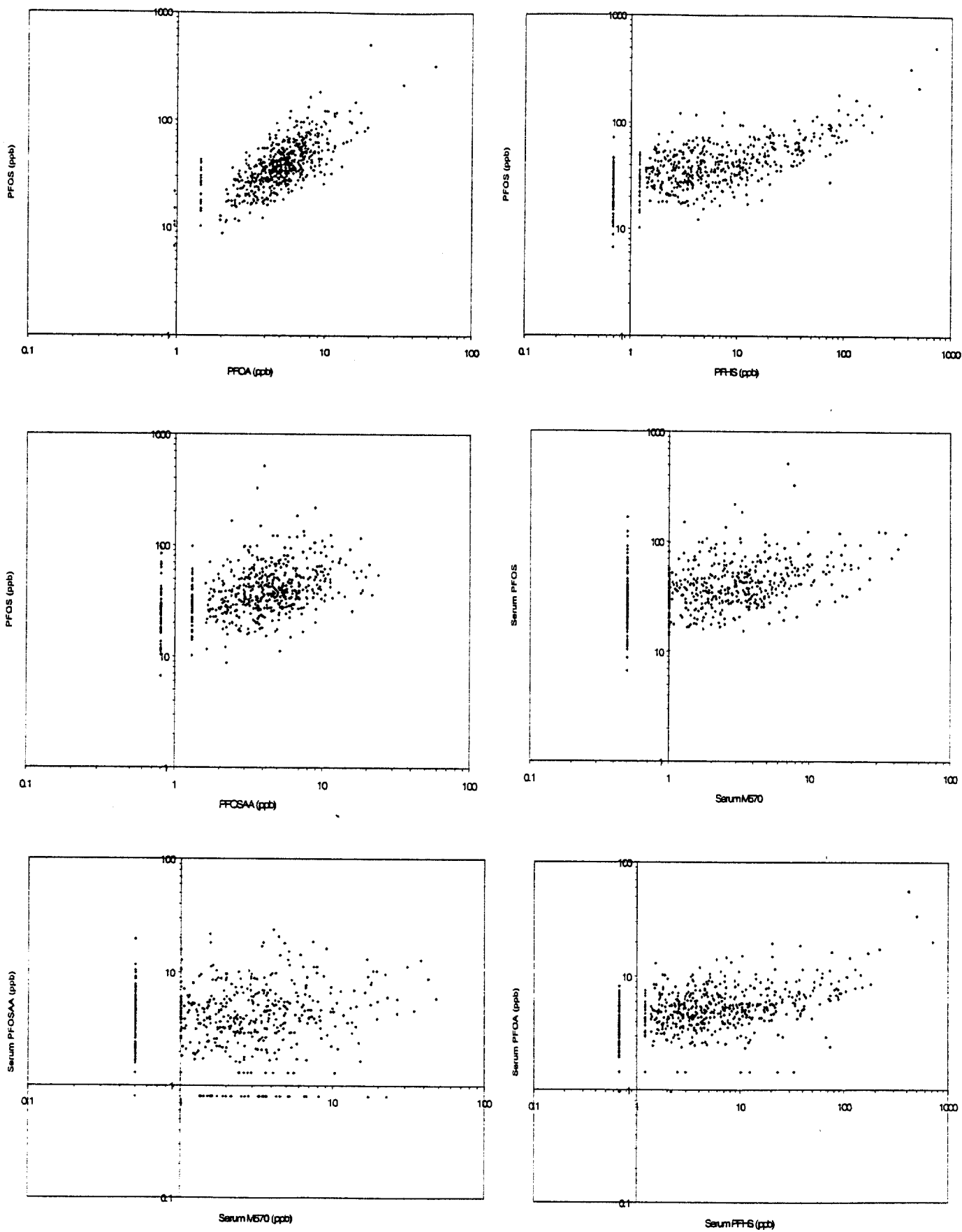
Figure 6. Comparison of Geometric Means and 95% Confidence Intervals for PFOS, PFOA, PFHS, PFOSAA and M570 for the Pediatric (N = 598), Adult (N = 645) and Elderly (N = 238) Studies
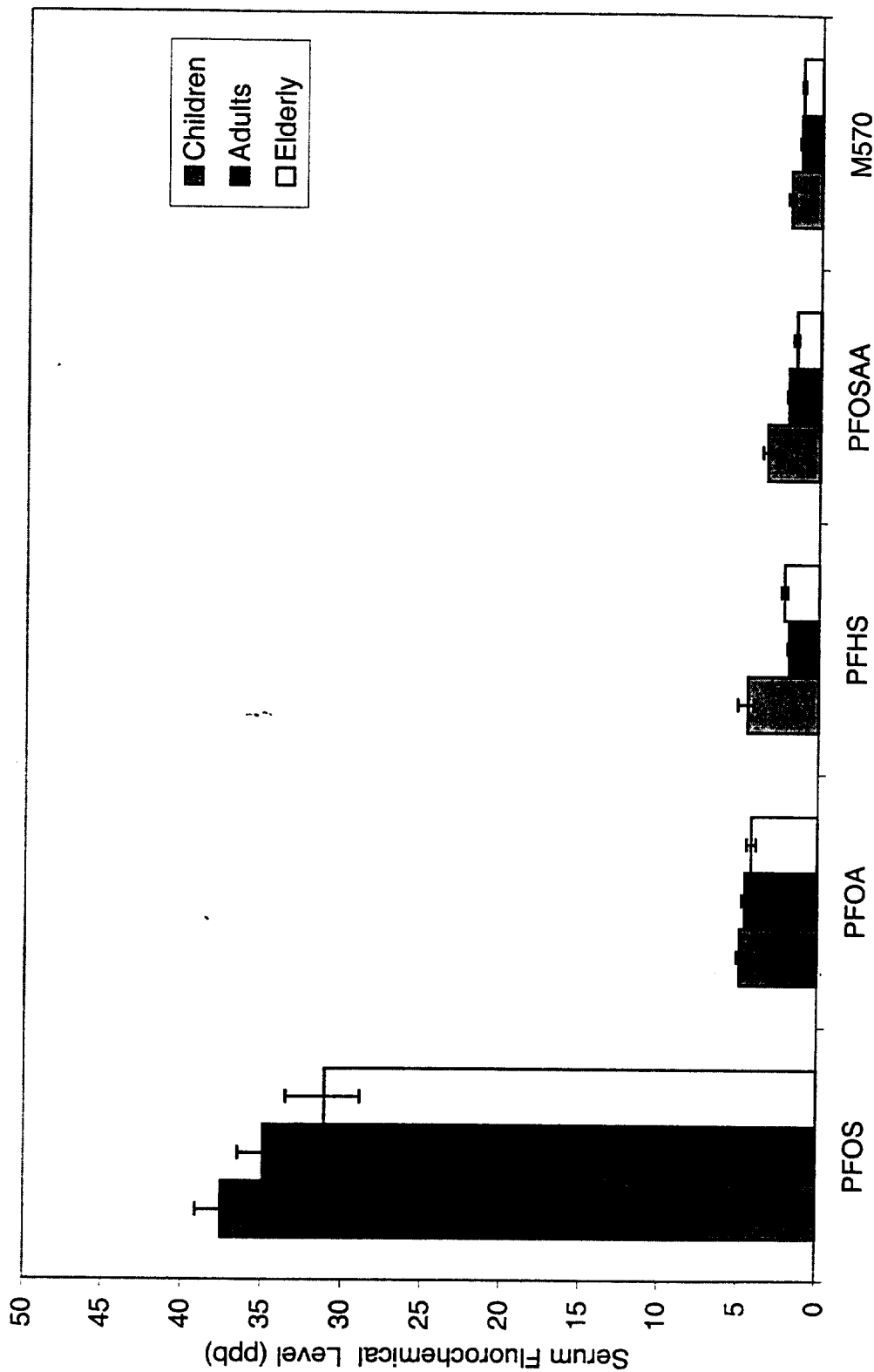
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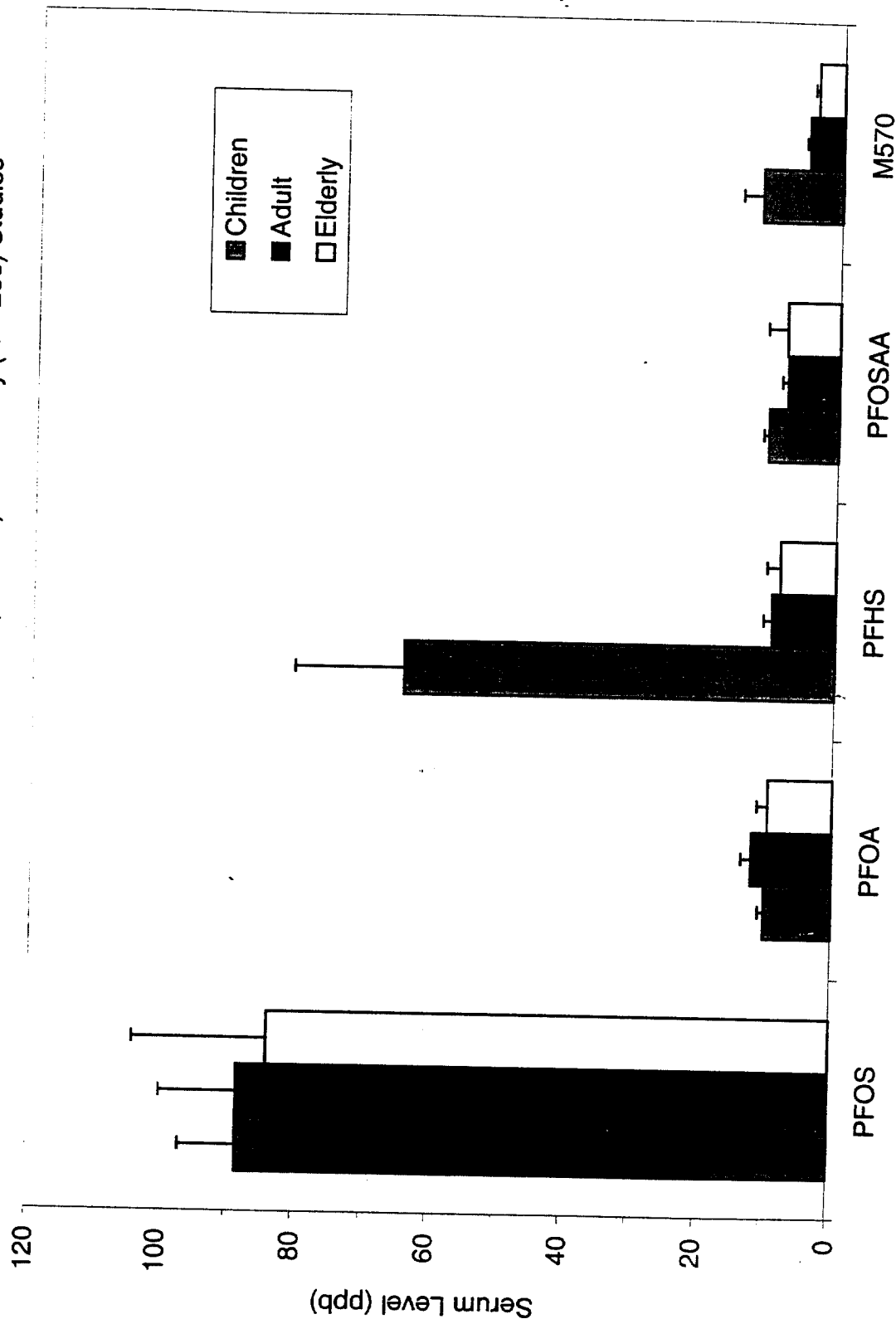
# Interim Report #2
## Epidemiology, 220-3W-05
## Medical Department
## 3M Company
## St. Paul, MN 55144

Date: January 11, 2002

Title: Determination of Serum Half-Lives of Several Fluorochemicals

Study
Start Date: November, 1998

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## ABSTRACT

This is the second interim report for an ongoing study, to determine the serum half-life of several fluorochemicals in humans by obtaining and analyzing multiple serial blood samples from 27 Decatur and Cottage Grove fluorochemical production plant retirees. A first interim report, issued in June 2000, suggested the serum half-life of PFOS in humans was likely in the range of 139-640 days, four-fold lower than the previously estimated range of 1000-1500 days (data derived from a different population of 3 workers). The serum half-life for PFOA in these 27 retirees appeared to be one year. However, the initial interim report was subsequently discounted in a 3M letter to the U.S. EPA, which noted that the first interim report analyzed the serum after each collection period with only one measurement per time period. In an effort to minimize experimental error, including systematic and random error in the analytical method, we initiated a more definitive analytical study on nine of the original 27 subjects. Serum samples collected from each of the nine subjects over four time points ($t_0$-$t_3$) spanning 180 days were measured in triplicate, with all time points from each subject being analyzed in the same analytical run.

The results from this second interim analysis suggest that the mean serum half-life for PFOS was 8.7 years (SD = 6.1; range 2.3-21.3). The mean serum half-life for PFOA was 4.4 years (SD = 3.5; range 1.5-13.5). The mean half-life for PFHS, which was deferred in the first interim report due to inconsistent results, was an uninterpretable -2.27 years (SD = 23.1; range -47.63-30.12). Half-life estimates for both PFOS and PFOA remain higher than those reported in laboratory animals.

This self-consistent data-set based on triplicate analysis of nine retirees allowed for an estimation of the serum fluorochemical half-life for PFOS, PFOA and PFHS with several caveats. Chief among these limitations are the following: no effort was made to determine or control for retiree re-exposure to PFOS, PFOA or PFHS during the study time-period, although retirees were not present in the production plant. Second, because PFOS is a metabolic product of compounds known to be present in the subject's blood, PFOS is possibly being produced in the body during the course of the study. Both

exposure to, and metabolic production of target analytes will lead to artificially long half-life estimations.

We will continue to collect retiree serum samples from the 27 subjects on an annual basis for the next two years. The samples will be stored frozen (-70°C) and not analyzed until sample collection is completed. At that time, it is our intention to analyze all study samples, beginning at $t_0$, during the same analytical run to assure that any experimental biases equally affect every serum sample. We do not foresee any further interim reports until the sample collection and laboratory analysis are completed.

# INTRODUCTION

In May, 2000, 3M announced that it would voluntarily cease producing the parent molecule, perfluorooctanesulfonyl fluoride (POSF) and its related products due to concerns about biopersistence and widespread exposure to human populations and wildlife (Hansen et al, 20001; Giesy and Kannan, 2001). These POSF-related products contain chemicals, either as intentional components or as impurities (residuals), which could degrade or metabolize to perfluorooctanesulfonate (PFOS), a compound that apparently does not undergo further metabolic or environmental degradation. PFOS and, in particular, various alkyl-substituted perfluorooctanesulfonamido compounds have been utilized in a wide variety of industrial and consumer products. In addition, 3M has manufactured salts of perfluorooctanoate (PFOA) and perfluorohexanesulfonate (PFHS) for industrial uses. These chemicals may also be found as residual impurities in POSF-related products.

Substantial toxicology and epidemiology research has been conducted on PFOS and PFOA (3M Company, 2000; Alexander et al, 2001a; 2001b; Butenhoff et al, 2001; Gilliland and Mandel, 1996; Kennedy, 1985; Kennedy et al, 1986; Olsen et al, 1998; 1999; 2000; Seacat et al, 2001a; 2001b). As the primary objective of this study was to quantify the serum half-life of PFOS and PFOA in humans, a brief synopsis follows which describes the pharmacokinetics of these two chemicals.

## Perfluorooctanesulfonate (PFOS)

In animals, PFOS distributes predominantly to the blood and liver, with liver concentrations being potentially several times higher than serum concentrations, depending on species and dose. After male rats were given single intravenous doses (4.2 mg/kg) of $^{14}$C PFOS it was found that the carbon-14 in liver and plasma represented 25

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and 3 percent of the dose, respectively, after 89 days (Johnson and Ober, 1979; Johnson et al, 1979). During the 89-day post-dose period, 30.2% of the administered $^{14}$C had been excreted in the urine and 12.6% had been excreted in the feces. Whole body elimination in the male rat appeared to be biphasic. Initial redistribution from the plasma yielded a plasma elimination half-life of 7.5 days. However, 89 days post-treatment, measurements of $^{14}$C indicated that the half-life of elimination exceeded 89 days in the male rat. Significant enterohepatic circulation was likely as cholestyramine administered in the diet to rats after a single intravenous dose of PFOS increased fecal elimination 9.5 times over control animals (Johnson et al, 1984).

In another study, cynomolgus monkeys were dosed by oral capsule with the potassium salt of PFOS at dosages of 0, 0.03, 0.15 and 0.75 mg/kg/day for 182 days (Seacat et al, 2001a). End-of-treatment PFOS concentrations averaged 0.12, 15, 75 and 172 ppm in serum and 0.12, 20, 64 and 334 ppm in the liver. Liver-to-serum PFOS ratios were comparable in all dose groups, with a range of 1:1 to 2:1. The serum PFOS elimination curves appeared to be multiphasic at the 0.75 mg/kg/day dose whereas at the 0.15 mg/kg/day dose elimination curves appeared more linear (0.03 mg/kg/day dose group was not a recovery group). Toward the end of the one year recovery period, the slope of the two recovery group elimination curves were similar suggesting that the PFOS elimination half-lives were approximately 200 days for both dose groups. Liver PFOS concentrations decreased in the same proportion as the serum concentrations. Liver to serum PFOS ratios showed no dose-related differences. Thus, the whole-body PFOS burden elimination rate was estimated to be proportional to the serum and liver elimination rates, in agreement with kinetic studies in the rat (Johnson et al, 1979).

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## Ammonium Perfluorooctanoate (PFOA)

Excretion rates of PFOA have been observed in rats. and found to be different by gender and route of excretion. Following single intravenous doses of ^{14}C-ammonium perfluorooctanoate in rats, Johnson et al (1984) reported that females excreted virtually all the administered ^{14}C within 1 day. Urinary excretion for males was about 50% of the dose by day 6 and 83% by day 36. Fecal ^{14}C excretion for females was 1.5% by 3 days and for males was 5.4% by 36 days. Rapid urinary excretion of ^{14}C following oral doses of ^{14}C PFOA was also shown to occur in pregnant rats.

Excretion rates also varied by species studied. Dupont studied excretion of radiolabeled PFOA in four species (DuPont, 1982). Excretion as a percentage of administered dose 120 hours after dosing was in the following order; female rat. male and female rabbit and male hamster (>99%); female hamster (60%); male rat (39%); male and female mice (21%). Of note, the administered dose and routes of exposure and excretion were not specified in this study report.

Rats and dogs responded to cholestyramine administration that increased PFOA excretion rates (Johnson et al, 1984). In male rats administered single intravenous doses of ^{14}C PFOA, cholestyramine (4% w/w in feed) increased cumulative 15-day fecal ^{14}C excretion 9.8-fold versus controls. Total ^{14}C excretion (feces plus urine) was also enhanced (84.3% of dose vs. 71.8% for controls). There was no difference between the renal clearances of ^{14}C in male and female dogs either before or after probenecid. Glomerular filtration rates of PFOA were similar in rats and dogs. (Hanhijarvi et al., 1982)

Elimination half-life has been experimentally determined in rats, dogs and primates. In rats, experimental results showed the same differential elimination rate by

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gender (i.e. female>male) as well as half-life differences by route of exposure. Following a single oral dose of $^{14}$C ammonium perfluorooctanoate in male rats, the plasma half-life was 4.8 days (Johnson et al. 1979). In female rats, over 90% of the intravenous dose was recovered in the urine within the first 12 hours. The whole body elimination half-life of PFOA in male and female rats was 15 days and less than one day, respectively, following a single 4-mg/kg-intraperineal dose (Vanden Heuval et al, 1991). The half-life of PFOA in the liver was 60 hours for female rats and 210 hours for male rats (Ylinen, et al 1990). The decreased excretion rate (i.e., increased elimination half-life) in males was also observed in dogs. The plasma half-life of PFOA was longer in male dogs (473 to 541 hours) than in females (202 to 305 hours) (Hanhijarvi et al., 1982).

The elimination half-life appears to be similar in male rats exposed to either inhalation or dermal exposure. Following repeated inhalation exposures to PFOA over a two-week period, blood organic fluoride levels in male rats showed a half-life of five to seven days (Kennedy et al., 1986). A blood half-life of five to seven days was seen following repeated dermal exposure in male rats (Kennedy, 1985).

Male cynomolgus monkeys received daily oral (capsule) doses of 0, 3 10 and 30 (reduced to 20) mg/kg/day of ammonium perfluorooctanoate for 26 weeks (Butenhoff et al 2001). Dose-dependent increases in liver weight occurred in all treated groups. Body weights were decreased in the 30/20 mg/kg dose group. Serum PFOA concentrations were variable, reached steady state and cleared in weeks and was not directly proportional to dose. Liver PFOA concentrations were also not directly proportional to dose and cleared within three months. At a six-month recovery sacrifice, the two 10 mg/kg monkeys had liver PFOA concentrations that returned to control levels. During the recovery period, serum half-lives of PFOA among the 10 mg/kg/day dose group (only treatment group in the recovery period) was estimated at less than 30 days.

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## Human Data

Although it was reported that the serum half-life of perfluorooctanesulfonate (PFOS) in humans may range between 1000 and 1500 days (Olsen et al 1999), this estimate was based on just 3 subjects with high variability due to different assays used over time. Published serum half-life of PFOA data is even more limited. Ubel et al (1980) reported an approximate half-life of 18 months for one ammonium perfluorooctanoate production worker whose serum organic fluorine level declined from 70 ppm to 40 ppm. Because of these limited data, a study was designed to quantify serum half-lives for several fluorochemicals, including PFOS and PFOA from retirees of the 3M Decatur and Cottage Grove fluorochemical production plants. A first interim report was issued which suggested the serum half-life of PFOS in humans may be less than originally expected (Burris et al 2000). However, this report was subsequently discounted in a letter (Zobel, 2001) to the U.S. EPA which noted that the first interim report analyzed samples collected from each subject at different time periods with only one measurement per time period. A more definitive analysis was designed to analyze a subset of the serum samples from each time-point in triplicate, with all time points from each subject being analyzed in the same analytical run. This self-consistent data-set would then allow for statistical evaluation of the precision of the measurement and assure that all systematic error inherent in the assay equally affected each sample used for half-life determination. The purpose of this second interim report is to present these findings.

## METHODS

This is the second interim report for this ongoing study and summarizes the study activity from November 1998 ($t_0$) through May, 2000 ($t_3$), a total of 4 measurements over an 18 month time period.

The overall research design is a prospective experimental study that obtains multiple serial blood samples from retirees throughout the course of a five-year period. Initially, the serum half-lives of seven fluorochemicals were considered: PFOS, PFOA, perfluorohexanesulfonate (PFHS), N-ethyl perfluorooctanesulfonamidoacetate (PFOSAA), N-methyl perfluorooctanesulfonamidoacetate (M570), perfluorooctanesulfonamide (PFOSA) and perfluorooctanesulfonamidoacetate (M556). However, most measurements of PFOSAA, M570, PFOSA and M556 were below the limit of quantitation and thus did not lend themselves to half-life calculations. Therefore, these four fluorochemicals have been discontinued for subsequent assay analyses.

### Study Participants

Twenty-four Decatur, Alabama retirees have voluntarily agreed to participate in this research effort involving multiple serum sample collection cycles. The retirees were invited to participate based on having prior work assignments in the chemical division. These participants were eligible for study selection if they retired from the 3M Decatur Chemical Plant between January 1, 1995 and January 1, 1998. Thirty-four individuals were initially identified and 24 individuals (71%) agreed to participate in the study. In addition, three retirees from Cottage Grove Chemical Division were invited to participate for a total of 27 study participants. Informed consent was obtained from each study participant prior to study initiation. The majority of the twenty-seven participants were

male, only two were female. All participants were long-term 3M employees having worked an average of 28 years at either the Decatur or Cottage Grove Chemical Division. The average age of the participants at the time of the first collection ($t_0$) was 60 years (range: 55-74). The mean number of months from retirement to the start of the study was 30 months (range: 5-130 months).

## Sample Collection and Intervals

To date, there have been five collection periods for the Decatur retirees: November 1998 ($t_0$), June 1999 ($t_1$), November 1999 ($t_2$), May 2000 ($t_3$) and February 2001 ($t_4$). Cottage Grove retirees have participated in four collection periods: June 1999 ($t_0$), November/December 1999 ($t_1$), May 2000 ($t_2$) and December 2000 ($t_3$).

The study participants were notified by letter of the sampling dates. Decatur retirees were invited to the Decatur Medical Department for sample collection. A laboratory technician or the Decatur site occupational health nurse performed the venipuncture. The serum samples were stored frozen until shipped on dry ice to the 3M Medical Clinic in St. Paul, Minnesota. Upon arrival in St. Paul, the samples were stored frozen until transferred to Northwest Bioanalytical Laboratory (NWB, Salt Lake City, UT), the designated contract laboratory. Cottage Grove retirees had their serum collected by the laboratory technician in the 3M Medical Clinic. Each participant completed a brief medical history questionnaire containing information about current medications and disease diagnoses. Participants have received letters informing them of their individual fluorochemical results, as the data became available from the laboratory.

## Analytical Method

High-performance liquid chromatography mass spectrometry/mass spectrometry (HPLC/MSMS) has been utilized to analyze all serum samples for PFOS. PFOA and PFHS using methods described by Hansen et al (2001). The analytical method for determining the concentration of specific fluorochemicals in human serum was quite complex and, briefly, involved the following steps. First, serum was diluted with water, buffer, and ion pairing reagent, and then liquid-liquid extracted with methyl tert-butyl ether (MTBE). The organic layer was removed, subsequently dried, and brought up to volume with a methanol/water diluent. The final sample diluent contained the fluorochemicals extracted from the serum along with many other MTBE soluble serum compounds. The extract was then analyzed with HPLC/MSMS and quantified against an extracted standard curve prepared by spiking an aliquot of human serum with varying levels of analyte and extracting the spiked fluorochemical in the same manner as the samples.

## Target Analytes

Summarized in Table 1 are the time periods and their corresponding sample identifications, collection dates, number of unique participants, target analytes, analytical laboratory, and matrix for the $t_0$ through $t_3$ data collections. At the end of each of the first three collection periods ($t_0$-$t_2$) a single serum sample from each study participant was submitted to NWB for fluorochemical analyses. All analytes were quantified by NWB the designated contract laboratory with the exception of M556 and M570 from the $t_0$ collection date. These analytes were quantified by 3M Environmental Laboratory. Analytes that measured above the limit of quantitation (ULOQ) were reanalyzed after dilution with rabbit sera. Twenty-seven retirees participated in the $t_1$ collection period.

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This was the first collection period that included the three Cottage Grove retirees who agreed to participate in the study. At $t_1$, a single sample for each retiree was analyzed by NWB for all seven analytes. All samples were quantitated versus a calibration curve prepared using human serum. Samples from the $t_3$ collection period were analyzed for only three of the seven fluorochemicals (PFOS, PFOA and PFHS) as the decision was made to discontinue analyzing for PFOSAA, M570, PFOSA and M556.

In an effort to minimize experimental error including systematic and random error in the analytical method we initiated a more definitive analytical study on nine of the 27 subjects. These nine individuals represented the range of PFOS and PFOA concentrations that had been measured in prior analyses. All nine subjects were Decatur retirees. Each had their serum from the four time periods ($t_0$ - $t_3$) measured in triplicate, with all four time-points analyzed in the same analytical run. This approach allowed for statistical evaluation of the precision of the measurement and assured that all experimental biases equally affected each sample used for half-life determination. This interim report summarizes the findings from these nine individuals. [Note: Single measurements were made on $t_3$ samples from the remaining 18 individuals but these are not included in this report due to the lack of simultaneous triplicate analyses of all time points ($t_0$- $t_3$). Samples collected at the $t_4$ time period (February 2001) for the 27 subjects are stored frozen at -70° C and will not be analyzed until data collection is completed.]


Reference Material

The reference material purity for PFOS, PFOA and PFHS was not available prior to the conduct of this study. Therefore, the reference material purity was initially assumed to be 100% for samples $t_0$-$t_2$. 3M contracted with Centre Analytical Laboratories, Inc. (State College, PA) to determine the absolute concentration of PFOS,

PFOA, and PFHS in the NWB stock solution used to prepare the analytical standards and controls for the reported sample analyses. Based on Centre Analytical's results. the concentrations of the calibration and quality control samples were corrected accordingly: PFOS (correction factor = 0.836); PFOA (correction factor = 0.909); and PFHS (correction factor = 0.855) for all analyses in this interim report.

Statistical Analyses

Serum half-lives were calculated using a one-compartmental model. The mathematical expression of this first-order process is a monoexponential equation, $C = C_0 \cdot e^{-k_{el}t}$, where C is the serum concentration, $k_{el}$ is the first-order elimination rate constant, and t is the time of blood sampling. The logarithmic equation for this exponential function has the general form of an equation describing a straight line: $\log C = \log C0 - (k_{el} \cdot t)/2.303$. The half-life of elimination can be calculated after $k_{el}$ has been determined from the slope of the line where $t_{1/2} = 0.693/k_{el}$.

RESULTS

Presented in Tables 2 and 3 are the individual and mean data, respectively, for the nine Decatur employees whose $t_0$-$t_3$ measurements were subjected to triplicate analyses during the same batch analyses. There are seven males and two females. The average age of the nine retirees at the study initiation ($t_0$) is 61 years (range 55-64; SD = 3.2). The mean number of years employed at Decatur is 27.7 years (range 20-33; SD = 4.8). Their number of months retired from Decatur average 18.9 months (range 5-38; SD = 10.5). Their average body mass index (BMI) is 27.9 (range 22.5-33; SD = 3.6). The mean PFOS, PFOA, and PFHS values at study initiation ($t_0$) were 0.89 ppm (range 0.11-3.53

ppm; SD = 1.07), 0.72 ppm (range 0.06-1.84 ppm; SD = 0.64), and 0.31 ppm (range 0.02-1.25 ppm; SD = 0.40), respectively. The mean serum half-life for PFOS was 8.67 years (range 2.29-21.3 years; SD = 6.12). The mean serum half-life for PFOA was 4.37 years (range 1.50-13.49 years; SD = 3.53). The mean serum half-life for PFHS was -2.27 years (range -47.63 - 30.12 years; SD = 23.14).

Multivariable regression analyses examined the influence of age, BMI, number of years worked or years since retired on the serum-half life. None of these variables were significant predictors of the serum half-lives.


DISCUSSION

The results from the first interim analysis suggested that the serum half-life of PFOS in humans was likely in the range of 139-640 days with a median half-life of 270 days. The serum half-life of PFOA appeared to be approximately one year. The half-life for PFHS was deferred because the assay measurement of PFHS was inconsistent (e.g., many subsequently collected samples were at higher levels than initial samples). There were several limitations noted in the first interim report, the most important being the limited data available, to date, and the range of the serum levels measured (PFOS range 0.2-2.0 ppm; PFOA 0.1-3.1 ppm). In addition, serum concentrations were based on a single measurement of each collected sample with the analytical measurements being conducted on different days and using slightly different analytical methods. This created an imprecise assessment of the serum fluorochemical concentrations. Finally, reference material purity was not determined until after the $t_0$-$t_2$ samples had been analyzed. The lack of adjustment for the reference material likely biased the fluorochemical values from 9-16% depending on the specific analyte. Because of these limitations, a subset of nine retirees had all their serum fluorochemical concentrations remeasured in triplicate.

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The results from this second interim analysis suggested that the mean serum half-life for PFOS was 8.7 years (SD = 6.1); however, the range of values 2.3 years to 21.3 years suggests variability that remains unaccounted for. This human serum half-life estimate is considerably higher than those reported in laboratory animals (Johnson and Ober 1979; Johnson et al 1979; Seacat et al 2001a; 2001b) although laboratory animal's serum half lives were not short (rats > 89 days; monkeys = 220 days). This may be due, in part, to the fact that serum concentrations in these nine retirees were an order of magnitude lower than the end-of-study PFOS concentrations used to calculate the serum half-lives in the cynomolgus monkey study (Seacat et al 2001a).

The mean serum half-life data for PFOA was 4.4 years (SD = 3.5) for these nine retirees, in contrast to the laboratory animal data that suggested serum PFOA half-lives of 5-7 days (male rat). The inconsistency between these human data and laboratory animal data remains unexplained.

We remain perplexed regarding the serum half-life of PFHS. Three of the nine subjects showed increased serum PFHS concentrations over time, which resulted in an uninterpretable average serum half-life mean of -2.3 years. We are unaware whether these workers may have received occupational or non-occupational exposures that may have distorted their findings. The remaining 6 subjects had mean serum half-lives that ranged between 2.9 and 30.1 years.

The refined approach used in this assessment for nine retirees allowed for an estimation of the serum fluorochemical half-life for PFOS, PFOA and PFHS with several caveats. First, while these retirees rarely entered the plant premises, no effort has been made to determine or control for retiree exposure to PFOS, PFOA or PFHS during the study time period ($t_0$ - $t_3$). However, exposure to these compounds could result in an artificially long determination of serum half-life. Because POSF-based fluorochemical

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production has been discontinued, the opportunity for future exposures is unlikely. Second, because PFOS is a metabolic product of compounds known to be present in these subjects blood, PFOS is likely being produced in the body during the course of the study, which again will artificially extend the measured half-life. Third, because subjects' blood contained concentrations of fluorochemicals which varied by a factor of 30, the data cannot be pooled or averaged unless the serum concentration decay curve shows first-order kinetics, which do not depend on concentration. Fourth, because subjects have a significant concentration of fluorochemical compounds in their blood in addition to PFOS, it is possible that unknown interactions or processes are at work which affect the actual or measured serum half-lives. Fifth, direct comparison of the PFOS half-life determined from humans and laboratory animals may not be sound due to potentially different protein binding sites and affinities. Finally, the data quality requirements specify that quality control samples and curve points must be within 20% of the actual concentration, therefore, a known systematic error of as much as +/- 20 % may be present and still satisfy the data quality criteria of the analytical method.

Since systematic error is additive, comparing two data-sets analyzed during different analytical runs or on different days may make such discrepancy increase to +/- 40%. This would not include random error. We attempted to remove systematic error by self-consistent data-set analysis of replicate samples. Any comparison of the results from this self-consistent data-set of nine subjects with the results obtained from the 18 subjects over 4 different time periods with systematic error would be difficult to interpret. Therefore, for this interim report, in order to reduce measurement error, we have chosen to report only the self-consistent data-set.

We will continue to collect retiree serum samples from the 27 subjects on an annual basis for the next several years. The samples will be stored frozen (-70°C ) and not

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analyzed until sample collection is completed. It is our intention to analyze all study samples, beginning at $t_0$, during the same analytical run to assure that any systematic biases equally affect every serum sample. We do not foresee any further interim reports until the sample collection and laboratory analyses are completed.

# REFERENCES

3M Company (2000). SIDS Initial Assessment Report Perfluorooctane Sulfonic Acid and its Salts. St. Paul (MN):3M Company, September 20. 2000.

Alexander BH (2001a). Mortality study of workers employed at the 3M Decatur facility. Final Report. Minneapolis (MN):University of Minnesota, April 26, 2001.

Alexander BH (2001b). Mortality study of workers employed at the 3M Cottage Grove facility. Final Report. Minneapolis (MN):University of Minnesota, April 26, 2001.

Burris J, Olsen G, Simpson C, Mandel J (2000) Determination of Serum Half-Lives of Several Fluorochemicals, Interim Report #1. St. Paul (MN):3M Company. June 8, 2000.

Butenhoff J, Costa G, Elcombe C, Farrar D, Hansen K, Iwai H, Jung R, Kennedy G, Lieder P, Olsen G, Thomford P (2001). Toxicity of ammonium perfluorooctanoate (APFO) in male cynomolgus monkeys after chronic oral dosing. Toxicol Sci (submitted).

DuPont Company, Haskell Laboratory (1982). Excretion and disposition of $^{14}$C-ammonium perfluorooctanoate in male and female rats, mice. hamsters, and rabbits. Unpublished Report.

Gilliland FD, Mandel JS (1996). Serum perfluorooctanoic acid and hepatic enzymes, lipoproteins and cholesterol: a study of occupationally exposed men. Am J Ind Med 129:560-568.

Giesy JP, Kannan K (2001). Global distribution of perfluorooctane sulfonate and related perfluorinated compounds in wildlife. Environ Sci Tech 35:1339-1342.

Hanhijarvi H, Phaug R, Singer L (1982). The sex-related difference in perfluorooctanoate excretion in the rat. Proc Soc Exp Biol Med 171:51-55.

Hansen KJ, Clemen LA, Ellefson ME, Johnson HO (2001). Compound-specific, quantitative characterization of organic fluorochemicals in biological matrices. Environ Sci Technol 35:766-770.

Johnson JD, Ober RF (1979). Absorption of FC-95-14C in rats after a single oral dose. St Paul (MN):Riker Laboratories, Inc. Project No., 890310200.

Johnson JD, Gibson SJ, Ober RE (1979). Extent and route of excretion and tissue distribution of total carbon-14 in rats after a single intravenous dose of FC-95-14C. St Paul (MN):Riker Laboratories, Inc. Project No. 8900310200.

Johnson JD, Gibson SJ, Ober RE (1984). Cholestyramine-enhanced fecal elimination of carbon-14 in rats after administration of ammonium [$^{14}$C]perfluorooctanoate or potassium [$^{14}$C]perfluorooctanesulfonate. Fund Appl Toxicol 4:972-976.

Kennedy G, Hall G, Brittelli J, Chen H (1986). Inhalation toxicity of ammonium perfluorooctanoate. Fd Chem Toxicol 24:1325-1329.

Kennedy G (1985). Dermal toxicity of ammonium perfluorooctanoate. Toxicol Appl Pharmacol 81:348-355.

Olsen GW, Gilliland FD, Burlew MM, Burris JM, Mandel JS, Mandel JH (1998). An epidemiologic investigation of reproductive hormones in men with occupational exposure to perfluorooctanoic acid. JOEM 40:614-622.

Olsen GW, Burris JM, Mandel JH, Zobel LR (1999). Serum perfluorooctane sulfonate and hepatic and lipid clinical chemistry tests in fluorochemical production employees. JOEM 41:799-806.

Olsen GW, Burris JM, Burlew MM, Mandel JH (2000). Plasma cholecystokinin and hepatic enzymes, cholesterol and lipoproteins in ammonium perfluorooctanoate production workers. Drug Chem Toxicol 23:603-620.

Seacat AM, Thomford PJ, Hansen KJ, Olsen GW, Case MT, Butenhoff JL (2001a). Subchronic toxicity studies on perfluorooctanesulfonate potassium salt in cynomolgus monkeys. Toxicol Sci (in press).

Seacat AM, Thomford PJ, Hansen KJ, Clemen LA, Butenhoff JL (2001b). Sub-chronic dietary toxicity of potassium perfluorooctanesulfonate in rats. Toxicology (submitted).

Ubel FA, Sorenson SD, Roach DE (1980). Health status of plant workers exposed to fluorochemicals, a preliminary report. Am J Ind Assoc J 41:584-589.

Vanden Heuvel J, Kuslikis B, Van Refelghem M, Peterson R (1991). Tissue distribution, metabolism and elimination of perfluorooctanoic acid in Male and Female Rats. J Biochem Toxicol 6(2):83-92.

Ylinen M, Koho A, Hanhijarvi H, Peura P (1992). Disposition of perfluorooctanoic excretion in the rat. Proc Soc Exp Biol Med 171:51-55.

Zobel L (2001). Serum Half-Life of Perfluorooctane Sulfonate. Letter to EPA. St. Paul (MN):3M Company, April 25, 2001.

Table 1  Chronology of Serum Sample Collection

| Time Period | Collection Date | Unique Participants | Samples per Participant | Target Analytes | Laboratory | Matrix |
|---|---|---|---|---|---|---|
| t0 (samples: 9276-9299) | 11/1998 | 24 (All Decatur Retirees) | 1 | PFOS, PFOA, PFHS, PFOSA, PFOSAA M556, M570 | NWB, 3M Environmental | Human, select samples diluted with rabbit sera |
| t1 (samples: 9406-9432) | 06/1999 | 27 (3 Cottage Grove Retirees agree to participate) | 1 | PFOS, PFOA, PFHS, PFOSA, PFOSAA M556, M570 | NWB | Human |
| t2 (samples: 9569-9595) ---- | 11/1999 | 27 | 1 | PFOS, PFOA, PFHS, PFOSA, PFOSAA M556, M570 | NWB | Human |
| t3 (samples: 9871-9897) | 05/2000 and Repeat analysis for: 11/1998, 06/1999, 11/1999 | 18 9 | 4* 12** | PFOS, PFOA, PFHS | NWB | Human |
| t4 | 02/2001 | 26 | 1 | *** | *** | *** |

\*      one serum sample from each of the following screening periods: t0, t1, t2, and t3

\*\*     three serum samples from each of the following screening periods: t0, t1, t2, t3

\*\*\*    samples stored frozen -20°

Table 2 Individual Data for Employees with Triplicate Analyses

| Employee/ Usual Job | Age | Years at Plant Retired | Months Retired | BMI | Gender | PFOS @ t0 (ppm) | ½ Life PFOS (years) | PFOA @ t0 (ppm) | ½ Life PFOA (years) | PFHS @ t0 (ppm) | ½ Life PFHS (years) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A (chemical operator) | 60 | 31 | 11 | 28.1 | Male | 3.5 | 13.1 | 1.8 | 13.5 | 1.3 | - 17.6 |
| B (supervisor) | 57 | 33 | 18 | 27.4 | Male | 1.1 | 3.7 | 0.7 | 4.3 | 0.4 | 30.1 |
| C (process engineer/ supervisor) | 64 | 27 | 38 | 28.1 | Male | 0.2 | 21.3 | 0.4 | 3.6 | 0.1 | - 47.6 |
| D (chemical operator) | 64 | 20 | 27 | 31.0 | Female | 0.4 | 4.4 | 1.7 | 3.1 | 0.1 | 7.1 |
| E (process operator) | 55 | 20 | 5 | 33.0 | Female | 1.3 | 12.0 | 0.9 | 3.9 | 0.2 | 11.0 |
| F (elect/control mech) | 63 | 27 | 11 | 24.4 | Male | 0.5 | 10.3 | 0.2 | 3.9 | 0.1 | 12.4 |
| G (cell operator) | 62 | 29 | 23 | 32.2 | Male | 0.3 | 6.6 | 0.4 | 3.5 | 0.6 | - 22.4 |
| H (QC technician) | 58 | 32 | 11 | 22.5 | Male | 0.6 | 2.3 | 0.2 | 1.5 | 0.2 | 2.9 |
| I (process engineer) | 62 | 30 | 26 | 24.8 | Male | 0.1 | 4.4 | 0.1 | 2.1 | 0.02 | 3.6 |

Table 3 Summary Half-Life Data for Employees with Triplicate Analyses

| | Age @ t0 | # Years at Plant | Months Retired | BMI t0 | PFOS @ t0 (ppm) | ½ Life PFOS (years) | PFOA @ t0 (ppm) | ½ Life PFOA (years) | PFHS @ t0 (ppm) | ½ Life PFHS (years) |
|---|---|---|---|---|---|---|---|---|---|---|
| Average | 61 | 27.7 | 18.9 | 27.9 | 0.9 | 8.7 | 0.7 | 4.4 | 0.3 | -2.3 |
| Minimum | 55 | 20 | 5 | 22.5 | 0.1 | 2.3 | 0.1 | 1.5 | 0.02 | -47.7 |
| Maximum | 64 | 33 | 38 | 33.0 | 3.5 | 21.3 | 1.8 | 13.5 | 1.3 | 30.1 |
| Std Dev | 3.2 | 4.8 | 10.5 | 3.6 | 1.1 | 6.1 | 0.6 | 3.5 | 0.4 | 23.1 |

# FINAL REPORT
## Epidemiology, 220-3W-05
## Medical Department
## 3M Company
## St. Paul, MN 55144

Date: October 11, 2001[*]

Title: A Cross-sectional Analysis of Serum Perfluorooctanesulfonate (PFOS) and Perfluorooctanoate (PFOA) in Relation to Clinical Chemistry, Thyroid Hormone, Hematology and Urinalysis Results from Male and Female Employee Participants of the 2000 Antwerp and Decatur Fluorochemical Medical Surveillance Program

Study
Start Date:     March 1, 2000

Protocol Number (not applicable)
IRB Approval
    Exempt     Expedited
      X

IRB Approval Date: (not applicable as these data are from a medical surveillance program)

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[*](Corrections made from previous version)

## ABSTRACT

The 3M fluorochemical medical surveillance program is conducted on a routine periodic basis at the company's Antwerp (Belgium) and Decatur (Alabama) fluorochemical manufacturing plants. In the most recent occurrence in 2000, there were 255 Antwerp employees (206 male and 49 female) and 263 Decatur employees (215 male, 48 female) who participated in the program. This represents approximately 75 percent and 50 percent of the eligible employees at these two locations, respectively. Seventy three percent of the participating Antwerp male employees and 75 percent of the Decatur employees were engaged in production activities. Only 12 percent of the participating Antwerp female employees were engaged in production activities compared to 63 percent of the Decatur female employees.

Employees' sera were quantitatively analyzed for PFOS (perfluorooctanesulfonate), PFOA (perfluorooctanoate), PFHS (perfluorohexanesulfonate), PFOSAA (N-ethyl perfluorooctanesulfonamidoacetate), M570 (N-methyl perfluorooctanesulfonamidoacetate), PFOSA (perfluorooctanesulfonateamide) and M556 (perfluorooctanesulfonamidoacetate) using high-pressure liquid chromatography/electrospray tandem mass spectrometry (HPLC/ESMSMS) and evaluated versus an extracted curve from a human serum matrix. A total organic fluorine index (TOF) was also determined by calculating the percent of each specific fluorochemical's molecular weight that was attributed to organic fluorine and multiplied by the ppm measured for each fluorochemical and then summed across all seven fluorochemicals.

Mean serum PFOS levels for Antwerp production and non-production male workers were 1.16 and 0.42 ppm, respectively. Among Decatur production and non-production male workers, their mean serum PFOS levels were 1.63 and 0.73 ppm, respectively. Mean serum PFOA levels for Antwerp male production and non-production workers were 1.28 and 0.34 ppm, respectively. Among Decatur male production and non-production workers, their mean serum PFOA levels were 2.34 and 0.59 ppm, respectively. The mean PFOS and PFOA levels for the Antwerp female employees (primarily nonproduction) were 0.13 ppm and 0.07 ppm, respectively. The mean PFOS and PFOA levels for Decatur female production and nonproduction employees were 0.93 and 1.23 ppm, respectively. Separate reports have been written which analyzed the employees' serum levels in relation to their job and building location work assignments as obtained from a self-reported work history questionnaire.

A standard set of hematological and clinical chemistry tests were analyzed. These included the following hematological tests: hematocrit (percent), hemoglobin (gm/dl), red blood cells (RBC, $1000/mm^3$), white blood cells (WBC, $1000/mm^3$) and platelet count ($1000/mm^3$); and the following clinical chemistry tests: alkaline phosphatase (IU/L), gamma glutamyl transferase (GGT, IU/L), aspartate aminotransferase (AST, IU/L), alanine aminotransferase (ALT, IU/L), total and direct bilirubin (mg/dl), blood urea nitrogen (BUN, mg/dl), serum creatinine (mg/dl), blood glucose (mg/dl), cholesterol (mg/dl), high density cholesterol (HDL, mg/dl) and triglycerides (mg/dl). Urinalyses were only assessed for Decatur employees via the standard urine microstick analysis, which tested for urine glucose, albumin and red blood cells. Six thyroid hormones were also assayed: thyroid stimulating hormone (TSH; $\mu$IU/ml); serum thyroxine (T4; $\mu$g/dL);

free thyroxine (free T4; ng/dL); serum triiodothyronine (T3; pg/mL); thyroid hormone binding ratio (THBR, %, previously referred to as T3 Uptake) and free thyroxine index (FTI).

Statistical analyses were conducted on the entire surveillance population as well as subgroups by gender, production worker (yes/no) and location. Univariate analyses categorized mean levels by serum PFOS quartile distributions. Multivariable regression was used to analyze the clinical chemistry and thyroid hormones as dependent variables in relation to the independent effects of PFOS, PFOA or TOF adjusted for several demographic variables (age, body mass index, number of alcoholic drinks per day, cigarettes smoked per day and years worked).

There was a modest positive association between PFOS or PFOA with cholesterol as well as a stronger positive association between PFOA and triglycerides. These associations are inconsistent with the known toxicological evidence that has shown the hypolipidemic (not hyperlipidemic) effect of PFOS (in rats and primates) and PFOA (in rats but no effect in primates) at dosages that produced serum PFOS or PFOA levels higher than those measured in this population. Therefore, it is unlikely the observed positive associations between PFOS or PFOA and lipids are causal. Because of the potential confounding positive association with serum triglycerides, this variable was added to the hepatic clinical chemistry models as an independent variable. In these models, no significant associations were observed with PFOS, PFOA or TOF in relation to alkaline phosphatase, GGT, AST, ALT or total bilirubin. Although T3 was positively associated with PFOA, no other thyroid hormones were associated with PFOS, PFOA or TOF; thus there is unlikely a causal explanation (e.g., hypothyroidism or

hyperthyroidism) for this positive T3 association with PFOA. Hematological and

urinalysis results were unremarkable.

In summary, the findings from the 2000 fluorochemical medical surveillance

program continue to suggest that Antwerp and Decatur fluorochemical production and

non-production employees do not have significant changes in serum cholesterol,

lipoproteins or hepatic enzymes that are consistent with toxicological findings in

laboratory animals. Limitations of the study include its cross-sectional design, the

voluntary participation rates and the lower levels of serum PFOS and PFOA measured

among these employees compared with those suspected to cause effects in laboratory

animals. A longitudinal analysis is reported separately for the fluorochemical medical

surveillance Antwerp and Decatur program data from 1994 through 2000.

# INTRODUCTION

The 3M fluorochemical medical surveillance program is conducted on a routine periodic basis at the company's Antwerp (Belgium) and Decatur (Alabama) fluorochemical manufacturing plants. Prior to 1994, total organic fluorine was measured rather than any specific fluorochemical analyte. Serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) have been routinely assayed since 1994/95 rather than total organic fluorine. An analysis of the 1994/95 and 1997 medical surveillance program data in relation to Antwerp and Decatur employees' serum PFOS levels have been reported elsewhere (Olsen et al, 1998a, 1999a). In the 1994/1995 medical surveillance program, a total of 178 employees participated (Antwerp = 88; Decatur = 90) and 149 employees participated in 1997 (Antwerp = 65; Decatur = 84). A total of 61 Antwerp and Decatur employees participated in both years. The Antwerp male employee population was significantly younger than that at Decatur, had lower Body Mass Indices (BMI) and had higher self-reported daily consumption of alcohol. In addition, the employees' clinical chemistry profiles were different for several tests. The Antwerp employee population had lower mean alkaline phosphatase and triglyceride values and higher total bilirubin and HDL values than the Decatur employee population. The findings from this prior epidemiologic analysis suggested that significant clinical chemistry and hematological abnormalities were not associated with serum perfluorooctanesulfonate (PFOS) levels up to 6 parts per million (Olsen et al 1998a; 1999a). Nor were there consistent associations reported between serum PFOS and several hormone tests including testosterone, estradiol and thyroid stimulating hormone (TSH). It was not possible to derive inferences from the few employees who had serum

PFOS levels $\geq$ 6 ppm. An important limitation of this prior analysis was the low voluntary participation of male employees (less than 50%) and insufficient sample size of female employees which prevented a separate analysis. Also, although serum perfluorooctanoate (PFOA) was measured, it was not included in the analyses.

Because the voluntary nature of the medical surveillance program may not provide for a complete understanding of the distribution of serum fluorochemical levels in the Decatur workforce, a random sample of 232 employees was selected for fluorochemical testing in the Fall, 1998. The distributions of employee serum PFOS and PFOA levels were comparable to the results reported in the voluntary Decatur medical surveillance program (Olsen et al 1999b). This finding suggested that the distribution of serum fluorochemical levels observed in the prior voluntary medical surveillance program likely reflected the distribution of serum PFOS and PFOA levels of all employees in the chemical plant.

Detailed discussions of the toxicology and epidemiology of PFOS and PFOA have been reported elsewhere (3M Company 2000; Alexander 2001a; 2001b; Butenhoff et al 2001: Gilliland and Mandel 1993;1996; Haughom and Spydevold 1992; Olsen et al 1998a: 1998b; 1999a; 2000; Pastoor et al 1987; Seacat et al 2001a; 2001b; Sohlenius et al 1993). For the purpose of brevity, this information will not be summarized in this Introduction. Suffice it to mention that for the purpose of employee medical surveillance, PFOS has been reported to be an inducer of peroxisome proliferation and hypolipidemia in rodents (Pastoor et al 1987; Ikeda et al 1987; Haughom and Spydevold 1992; Seacat et al 2001a: Sohlenius et al 1993 ) and primates (Seacat et al 2001b). PFOA has been inconsistently reported to produce hypolipidemia in rodents (Pastoor et al 1987;

Haughom and Spydevold 1992;) and not in primates (Butenhoff et al 2001). The mechanism of action pertaining to this hypolipidemia remains to be fully elucidated.

The purpose of this report was to conduct a cross-sectional analysis of the 2000 fluorochemical medical surveillance program for Antwerp and Decatur male and female employees. Unlike the earlier report for Antwerp and Decatur employees which only analyzed for PFOS (Olsen et al 1998a; 1999a), the present study examined associations for both PFOS and/or PFOA as well as a calculated measure for total organic fluorine (TOF). Longitudinal analyses of employees who participated from 1994/95 through 2000 were not analyzed as this was a focus of a separate analytical report (Olsen et al 2001a).

## METHODS

The fluorochemical medical surveillance program is available, on a voluntary basis, to all Antwerp and Decatur chemical plant employees and those site employees who may work in the chemical plant area. In 2000, approximately 340 Antwerp and 500 Decatur chemical plant and site employees were eligible to participate. In addition to the fluorochemical testing program, a standard battery of clinical chemistry, pulmonary function and urinalysis (Decatur only) tests were performed on employees. In addition, several thyroid hormones were measured. A site-specific work history was also administered to all employee participants. Analyses of these self-reported workplace questionnaire data in conjunction with the employees' serum fluorochemical levels have been reported elsewhere for Antwerp (Olsen et al 2001b) and Decatur (Olsen et al, 2001c).

## Hematology, Clinical Chemistry and Urinalysis

Allina Laboratory Services (St. Paul, Minnesota) performed the standard hematological and clinical chemistry tests. These included the following hematological tests: hematocrit (percent), hemoglobin (gm/dl), red blood cells (RBC, 1000/mm$^3$), white blood cells (WBC, 1000/ mm$^3$) and platelet count (1000/ mm$^3$); and the following clinical chemistry tests: alkaline phosphatase (IU/L), gamma glutamyl transferase (GGT, IU/L), aspartate aminotransferase (AST, IU/L), alanine aminotransferase (ALT, IU/L), total and direct bilirubin (mg/dl), blood urea nitrogen (BUN, mg/dl), serum creatinine (mg/dl), blood glucose (mg/dl), cholesterol (mg/dl), high density cholesterol (HDL, mg/dl) and triglycerides (mg/dl). Urinalyses were only assessed for Decatur employees via the standard urine microstick analysis which tested for urine glucose, albumin and red blood cells.

## Thyroid Hormones

Six thyroid tests were conducted by LabCorp (Kansas City, MO): thyroid stimulating hormone (TSH; $\mu$IU/ml); serum thyroxine (T4; $\mu$g/dL); free thyroxine (free T4; ng/dL); serum triiodothyronine (T3; pg/mL); thyroid hormone binding ratio (THBR, %, previously referred to as T3 Uptake) and free thyroxine index (FTI). TSH, free T4 and T3 were determined by an immunochemiluminometric assay (ICMA). T4 and THBR were determined by a cloned enzyme donor immunoassay (CEDIA). FTI was calculated by multiplying T4 and THBR.

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## Fluorochemical Analyses

Sera samples were extracted using an ion-pairing extraction procedure (Hansen et al, 2001). The extracts were quantitatively analyzed for PFOS (perfluorooctanesulfonate), PFOA (perfluorooctanoate), PFHS (perfluorohexanesulfonate), PFOSAA (N-ethyl perfluorooctanesulfonamidoacetate), M570 (N-methyl perfluorooctanesulfonamidoacetate), PFOSA (perfluorooctanesulfonateamide) and M556 (perfluorooctanesulfonamidoacetate) using high-pressure liquid chromatography/electrospray tandem mass spectrometry (HPLC/ESMSMS) and evaluated versus an extracted curve from a human serum matrix. Endogenous levels of certain fluorochemical were determined in the standard serum matrix and additional fluorochemical was spiked into the matrix. The total amount of each specific fluorochemical (endogenous + spiked) was used to construct an extracted standard curve. All serum fluorochemical analyses were determined by Northwest Bioanaltyical Laboratory Inc. (Salt Lake City, UT). A description of the distribution of the serum fluorochemical levels is reported elsewhere for Antwerp (Olsen et al, 2001b) and Decatur (Olsen et al, 2001c).

For Antwerp, all employee serum values for PFOS and PFOA values were above the lower limit of quantitation (LLOQ). There was one employee (0.3 percent) with a PFHS value below the LLOQ (0.0027 ppm) and one employee (0.3 percent) with a M570 below the LLOQ (0.0057 ppm). There were 111 employees (44 percent) with PFOSAA values below the LLOQ (0.006 ppm); 88 employees (35 percent) were below the LLOQ (0.001 ppm) for PFOSA; and 13 employees (5 percent) were below the LLOQ (0.0043

ppm) for M556. For Decatur, all employee serum values for PFOS, PFHS, PFOA and

M570 were above the respective lower limit of quantitation (LLOQ). There were 8 (3

percent) employees with PFOSAA values below the LLOQ (0.006 ppm); 111 employees

(42 percent) were below the LLOQ for PFOSA (0.001 ppm); and 13 employees (5

percent) were below the LLOQ for M556 (0.0043 ppm). For statistical analysis purposes,

serum fluorochemical values that were less than the LLOQ were assumed to be the

midpoint between zero and the LLOQ.

A total organic fluorine index (TOF) was determined by calculating the percent of

each specific fluorochemical's molecular weight that was attributed to organic fluorine

(PFOS (64.7%); PFHS (61.9%); PFOA (69.0%); PFOSAA (55.3%); PFOSA (64.7%);

M570 (56.6%) and M556 (58.1%)) multiplied by the ppm measured for each

fluorochemical and then summed across all seven fluorochemicals.

## Data Analyses

Serum PFOS and PFOA levels were the predominant fluorochemicals as the other

five analytes were measured at considerably lower levels (Olsen et al 2001b; 2001c);

therefore, PFOS and PFOA were the only two specific fluorochemicals analyzed as

explanatory variables in regression models. TOF was also considered in the analyses

which took into account these other analytes in an aggregate index (see above definition).

Descriptive simple and stratified analyses, Pearson correlation coefficients, ANOVA and

multivariable regression were used to evaluate associations between PFOS, PFOA and

TOF and each hematological and clinical chemistry test and thyroid hormone assay. For

stratified analyses, employees were divided into quartiles of their serum PFOS

distribution. Age, body mass index, current alcohol consumption (drinks per day) and cigarette use (cigarettes smoked per day), years worked at Antwerp or Decatur, and type of job (production versus non-production) were potential confounding factors that were considered in the analyses. Production jobs included cell operators, chemical operators, mill operators and crew supervisors. Non-production jobs included engineers, QA/AC laboratory and research workers, secretaries and managers.

Multivariable regression models were fitted with PFOS and/or PFOA analyzed as a continuous variable(s). Significance of coefficients was considered at $p < .05$. Natural log transformations of the dependent variables were performed, when necessary, to normalize variables and to enhance model fit. Study results were analyzed using the SAS System (1990).

RESULTS

Altogether, there were 255 Antwerp employees (206 male and 49 female) and 263 Decatur employees (215 male, 48 female) who participated in the 2000 fluorochemical medical surveillance program (Table 1). Seventy three percent of the Antwerp male employees and 75 percent of the Decatur employees worked in production activities. Only 12 percent of the Antwerp female employees worked in production activities compared to 63 percent of the Decatur female employees.

Provided in Table 2 are the mean PFOS, PFOA and TOF values, demographic values and clinical chemistry and thyroid values for male employees stratified by location and production or non-production work activities. Regardless of the production categorization, Antwerp male employees compared to Decatur employees had lower

serum PFOS and PFOA levels; were significantly younger; had lower mean BMIs; worked fewer years; drank, on average, more alcoholic beverages per day; had higher mean HDL and total bilirubin values; and had lower mean triglyceride, alkaline phosphatase, GGT, AST and ALT values. Mean thyroid hormone values tended to be higher among Antwerp employees. All mean values were within reference ranges. Comparable findings were observed for Antwerp female employees compared to Decatur female employees (Table 3).

Given the differences between Antwerp and Decatur employees, univariate analyses were initially stratified by location. Antwerp data, stratified by gender and production, are provided in Tables 4 through 12. In a similar fashion Decatur employee data are provided in Tables 13-24. The Decatur data also include employee urinalysis results.

Antwerp production male employee data (n = 150), stratified by quartile of serum PFOS distribution, is presented in three sequential tables for clinical chemistry (Table 4) and thyroid hormones (Table 5) and hematology (Table 6) results. The highest quartile ($4^{th}$) mean serum PFOS level was 2.61 ppm (range 1.76 - 6.24 ppm) compared to the lowest quartile ($1^{st}$) mean serum PFOS level of 0.29 ppm (range 0.04 - 0.41 ppm). Production workers in the highest quartile of serum PFOS levels were older and worked more years at Antwerp. There were no significant mean differences between the quartiles for BMI, cigarettes smoked or drinks per day. There was only one significant difference between the four quartile levels for any clinical chemistry, thyroid hormone or hematology comparisons. This significant difference was the comparison of the mean BUN value between the $1^{st}$ and $3^{rd}$ quartiles.

In a similar fashion for the 56 non-production Antwerp male employees, their clinical chemistry, thyroid hormone and hematology results are presented in Tables 7, 8 and 9, respectively, for their quartile distribution of serum PFOS. In this analysis, the highest quartile had a mean serum PFOS level of 0.90 ppm (range 0.49 - 1.76) compared to a mean of 0.13 ppm (range 0.05-0.20 ppm) in the lowest quartile. No significant mean differences were observed for demographic (Table 7), clinical chemistry (Table 7), thyroid hormone (Table 8) or hematology (Table 9) comparisons between the serum PFOS quartile distributions.

Among the 49 Antwerp production and non-production female employees analyzed as a group (Table 10), the highest quartile mean serum PFOS level was 0.26 ppm (range 0.15 - 0.55) compared to the lowest quartile mean serum PFOS level of 0.06 ppm (range 0.04 - 0.08 ppm). The highest serum PFOS quartile did not significantly differ demographically than the other three quartiles (Table 10). The lower three quartiles had some significant differences between themselves for the mean comparisons of years worked and drinks per day. Only one clinical chemistry, BUN, was significantly different between the quartiles as the 3rd and 4th quartiles had higher mean BUN values than the 1st quartile. All mean values were within reference ranges. No significant mean thyroid hormone (Table 11) or hematology (Table 12) difference was observed between the quartiles.

A total of 161 Decatur production male employees were stratified based on their quartile distribution of serum PFOS (Table 13). The highest quartile had a 3.22 ppm mean serum PFOS level (range 2.31 - 10.06) compared to 0.55 ppm mean serum PFOS level in the lowest quartile. There were no significant mean demographic differences

between the four quartiles and the only clinical chemistry test that was significantly different was ALT (Table 13). The highest quartile had a significantly higher mean ALT level (44 IU/ml) compared to the 1st (33 IU/ml), 2nd (32 IU/ml) or 3rd (33 IU/ml) quartiles. There were no significant mean differences for the Decatur male production employee quartile distributions for thyroid hormones (Table 14), hematology (Table 15) or urinalysis (Table 16) results.

Among the 54 Decatur non-production male employees (Table 17), their highest quartile mean serum PFOS level was 1.66 ppm (range 1.00 - 2.95 ppm) compared to the lowest quartile mean of 0.19 ppm (range 0.06 - 0.29 ppm). The highest quartile worked almost twice as long as the lowest quartile (Table 17). There were no significant differences in other demographics, clinical chemistries (Table 17), thyroid hormones (Table 18), hematology (Table 19) or urinalysis (Table 20) results among the quartile distributions.

Among the 48 Decatur production and non-production female employees (Table 21), the highest quartile had a mean serum PFOS level of 2.04 ppm (range 1.38 - 3.62 ppm) compared to the lowest quartile mean serum PFOS level of 0.20 ppm (range 0.06 - 0.31 ppm). There were no significant differences between the quartiles in relation to demographics (Table 21), clinical chemistries (Table 21) or thyroid hormones (Table 22). The third quartile had a significantly lower mean platelet count than the 1st quartile (Table 23); however, the fourth quartile was not significantly lower than the 1st quartile. Urinalysis findings did not differ by quartile (Table 24).

Presented in Table 25 are the number (and percentage) of Antwerp or Decatur employees which had above reference range values for hepatic clinical chemistry tests.

These findings in Table 25 are stratified by serum PFOS quartile distribution within each of the gender and production/non-production categories. Because each sub-population has a different serum PFOS quartile distribution, comparisons should only be done within each location-, production- and gender-specific category. Also presented is the number and percentage of employees who had one or more liver enzyme and bilirubin tests above the reference ranges (see aggregate total liver panel). The percentage of Antwerp employees whose liver enzyme tests were above reference range values was comparable for production and non-production male employees. Among Decatur employees, there was a higher percentage of production male employees in the 4th quartile for ALT, GGT and the total liver panel than the other quartiles. For non-production male employees, the highest percentages occurred in the second or third quartiles. Neither Antwerp or Decatur female employees had percentages consistent with any trend in the quartile distributions.

Provided in Tables 26 and 27 are the serum PFOS quartile distributions for the combined 421 Antwerp and Decatur production and non-production male employees. The highest quartile (4th) had a mean serum distribution of 2.69 ppm (range 1.69 – 10.06 ppm) compared to 0.27 ppm mean (range 0.04 – 0.42 ppm) compared to the lowest (1st) quartile distribution. It is important to note that the number (and percentages) of Antwerp versus Decatur employees in each of these four quartiles differ (see footnote to Table 26). In the lowest (1st) quartile, there is a greater percentage of Antwerp than Decatur male employees and more non-production than production employees. In the subsequent higher serum PFOS quartiles, the percentage of Decatur production male employees increased and the percentage of non-production male employees, whether

from Antwerp or Decatur, decreased. These differences were also reflected in the demographics between quartiles. For example, demographically the trend from the lowest to highest quartile increased with age, BMI and years worked and decreased with the mean number of alcohol drinks per day. Likewise, the means of the clinical chemistry and thyroid hormone tests were reflective of the higher percentage of Antwerp employees in the lower quartiles and higher percentage of Decatur employees in the higher quartiles. Mean triglyceride and alkaline phosphatase levels were lower and total bilirubin levels were higher in the lowest quartile compared to the highest quartile. For thyroid hormones, T3 was lower in the 1st quartile compared to the 4th quartile and THBR was significantly higher.

Combined analyses of Antwerp and Decatur production and non-production female employees (Tables 28 and 29) presented a similar distribution of employees by location and production pattern as was observed with the production and non-production male employees (Tables 26 and 27). Antwerp female employees predominated in the lowest quartile and Decatur female employees predominated in the highest quartile. This distribution difference is then seen with the lower mean age, BMI and alkaline phosphatase findings and the greater number of drinks per day and higher total bilirubin levels in the lowest quartile compared to the highest quartile. Also observed was a lower mean GGT and blood glucose level in the lowest quartile when compared to the highest quartile. There were no thyroid hormone differences between the quartile distributions (Table 29).

Summarized in Table 30 are the combined number of Antwerp and Decatur employees (and percentages) who had hepatic clinical chemistry tests above reference

range values stratified by quartile of the serum PFOS distribution. Among male employees, twelve percent of the employees had above reference range values for ALT and GGT in the 4th quartile compared to 4 to 8 percent in the 1st through 3rd quartiles. For the total liver panel, 23 percent of the male employees had one or more liver clinical chemistry tests above the reference range value compared to 14 to 16 percent in the lower three quartiles. No differences were observed within the female employee population. These percentages were not adjusted for potential confounding factors (e.g., BMI).

Because the higher liver enzyme function test results in the 4th quartile might be confounded by demographics (higher BMI, older age) and/or clinical chemistry tests (triglycerides) reflective of dietary differences, multivariable regression analyses were conducted on the combined Antwerp and Decatur male employee participants. Each regression model had the following variables: production job (yes = 1; no = 0); Antwerp/Decatur (1 = Antwerp; 0 = Decatur); age, BMI, cigarettes per day, drinks per day and years worked. For the analyses that involved hepatic clinical chemistry tests, triglycerides was also considered a potential explanatory variable. Regression models analyzed serum PFOS, serum PFOA, serum PFOS and PFOA, and total organic fluorine (TOF).

Provided in tables 31 through 34 are the analyses for these fluorochemical comparisons in relation to their effect on cholesterol, adjusted for the other explanatory variables. Serum PFOS was positively associated with cholesterol although its explanation of the variability of cholesterol in the model was less than 1 percent (see partial $R^2$). (Note: This positive association is opposite that of the well-established negative association between serum cholesterol and PFOS that have been shown to occur

in toxicological studies at threshold serum doses that were approximately 2 orders of magnitude higher than those serum PFOS levels observed in these employees.) Like PFOS (Table 31), there were positive significant associations each for PFOA (Table 32) and TOF (Table 34) with cholesterol but the model that jointly examined the effects of PFOS and PFOA found neither to be significant (Table 33). Again, this is contrary to the toxicological research that has shown PFOA lowers serum cholesterol. Age and drinks per day were significant variables in the model with cholesterol. PFOS and TOF were not significantly associated with HDL, but PFOA was significantly negatively associated (Tables 35 through 38). As to be expected, BMI and drinks per day were strongly associated with HDL. Analysis of triglycerides showed PFOS, PFOA and TOF were positively associated (Tables 39 through 42). PFOA appeared to be the more significant predictor than PFOS. (Note: PFOS and PFOA have decreased serum triglyceride levels at toxicological doses, not increased serum triglyceride levels.) Age, BMI and cigarettes smoked per day were significant variables in the triglyceride models found in Tables 39 through 42. Provided in Figures 1 through 3 are scatter plots of the simple linear regressions between the natural log of serum triglycerides and PFOA for Antwerp male, Decatur male and Antwerp and Decatur female employees.

Multivariable regression model results for the hepatic clinical chemistry analyses are found in Tables 43 through 62. Because of the potential confounding positive association with serum triglycerides, this variable is added to these models. No significant associations were observed with PFOS, PFOA and TOF in relation to alkaline phosphatase (Tables 43 through 46), GGT (Tables 47 through 50) or AST (Tables 51 through 54). Although PFOS or PFOA were not significantly associated with ALT

(Tables 55 – 57), TOF was positively associated with ALT (Table 58). PFOS, PFOA or

TOF were not significant predictors of total bilirubin (Tables 59-62).

Multivariable regression analyses of the thyroid hormones resulted in no

significant associations of PFOS, PFOA or TOF with TSH (Tables 63 – 66), T4 (Tables

67 – 70), Free T4 (Tables 71 – 74), THBR (Tables 75 – 78) or FTI (Tables 79 – 82).

PFOS, PFOA and TOF were positively associated with T3 although contributed

minimally to the variation explained in the model (see partial $R^2$).

## DISCUSSION

Although voluntary participation rates ranged from 53 percent (Decatur) to 75

percent (Antwerp), the 2000 fluorochemical medical surveillance program had the most

(in absolute numbers) employee male and female participants ever for both locations.

This is likely due to a combination of factors including 1) greater knowledge of the

collective (individual and research) value of the fluorochemical medical surveillance

program; 2) employee awareness about the persistence and prevalence of PFOS in human

tissue and the environment; and 3) the company's May 16, 2000 phase out announcement

that it would cease production of perfluorooctanyl chemistry in certain repellents and

surfactants by the end of 2000.

Serum PFOS and PFOA levels were comparable to those previously reported for

employees at these manufacturing operations. Serum levels appeared to be log normally

distributed with the highest values for PFOS at 10 ppm. This upper tail of the serum

PFOS distribution was also reported in a random sample analysis of Decatur employees

conducted in 1998 (Olsen et al 1999b). Separate reports examine the employees' serum

PFOS, PFOA, PFHS, PFOSAA, M570, PFOSA and M556 levels measured in the 2000

fluorochemical medical surveillance program with their workplace operations in Antwerp

(Olsen et al, 2001b) and Decatur (Olsen et al, 2001c).

We continued to observe consistent differences between Antwerp and Decatur

employees regarding their demographics and lifestyle differences. In particular, Antwerp

male employees, on average, were younger (and thus worked less), had much lower

BMIs and drank more alcoholic beverages than their Decatur counterparts. All three

differences can be important confounding variables when analyzing lipid and hepatic

clinical chemistry tests. We have also consistently seen higher total bilirubin values

among Antwerp employees since 1995 which may be partially attributable to a greater

prevalence of Gilbert's syndrome (Olsen et al 1998a; 1999a).

An inconsistent finding from these aggregate analyses was the positive

associations in the multivariable models reported between PFOS and serum cholesterol

and PFOA and serum cholesterol and triglycerides. There is a substantial body of

toxicological literature to suggest these associations are spurious because PFOS (in rats

and primates) has been reported to decrease serum cholesterol and triglyceride levels (3M

Company 2000; Haughom and Spydevold 1992; Ikeda et al 1987; Pastoor et al 1987;

Seacat et al 2001a; 2001b; Sohlenius et al 1993). On the other hand, there is inconsistent

evidence for hypolipidemia with PFOA in rodents (Pastoor et al 1987; Haughom and

Spydevold 1992) and no effect observed in primates (Butenhoff et al 2001). In primates,

there was no association observed between PFOA and cholesterol or triglycerides

(Butenhoff et al 2001). There is no toxicological evidence that at the serum PFOA levels

observed in our medical surveillance program that PFOA would have resulted in

hyperlipidemic associations. In addition, the PFOA levels observed among Antwerp and Decatur employees in 2000 was lower than those measured in 3M's Cottage Grove manufacturing employees whose serum PFOA levels have been assayed as high as 100 ppm. Hypolipidemic or hyperlipidemic effects have not been associated with serum PFOA levels among these Cottage Grove employees (Gilliland and Mandel 1996; Olsen et al, 2000). Most recently, the 2000 Cottage Grove fluorochemical medical surveillance program analysis again showed no association between serum PFOA levels and serum cholesterol or triglycerides (as seen in Figure 4). (Note: The serum PFOA levels graphed in Figure 4 are substantially higher than those cited in Figures 1 through 3 for the Antwerp and Decatur male and female employees.) We therefore believe that it is highly unlikely that these are causal associations observed in the 2000 fluorochemical medical surveillance data between PFOA and serum cholesterol and triglycerides.

Previous toxicological and epidemiological research has also not suggested positive associations between elevated serum liver enzymes results and serum PFOS or PFOA that were at the levels observed in the Antwerp and Decatur employee population (3M Company, 2000; Butenhoff et al 2001; Gilliland and Mandel 1996; Olsen et al 1998a; 1999a; 2000; Seacat et al 2001a; 2001b). In this 2000 fluorochemical medical surveillance program we observed, among Decatur production employees, a significantly greater mean ALT among those workers in the highest serum PFOS quartile distribution compared to the other three quartiles. This highest quartile of Decatur employees also had the greatest percentage of employees with ALT (28%) and GGT (15%) values above the reference range as well as the total liver panel (35%). A comparable percentage (36%) was observed among Decatur non-production employees in the second lowest

quartile with one or more hepatic clinical chemistry tests above the reference range. When male employees were combined by production status and location (as seen in Table 30), we reported an upward trend in the percentage of employees in the highest quartile with values above the reference range for ALT (12%), GGT (12%) and total liver panel (23%). However, after adjusting the employees' individual liver function values by potential confounding factors including age, BMI, number of alcoholic drinks per day, cigarettes per day and serum triglyceride values, we found no association between liver function values and PFOS or PFOA. We therefore suspect that the univariate associations were influenced by known confounders of liver function analyses

A battery of thyroid hormone tests were included in the 2000 fluorochemical medical surveillance program due to preliminary, albeit biologically inconsistent, findings in toxicological studies that have yet to be completed. Our surveillance data do not suggest any biologically significant associations between thyroid hormones and employees' measured serum PFOS, PFOA or calculated TOF levels.

A retrospective cohort mortality study of Decatur employees from 1961-1997 reported 3 deaths from bladder cancer compared to 0.2 expected in the subgroup of workers with the highest potential exposure to perfluorooctanesulfonyl fluoride (POSF)-based chemistry and materials (Alexander 2001b). It was not determined whether this association was fluorochemical-related or possibly due to other non-fluorochemical occupational or non-occupational exposures. An analysis of episode of cares (Olsen et al 2001d) reported a higher reoccurrence of cystitis among female Decatur chemical plant workers than their counterparts in the film plant although the actual prevalence of unique individuals with episodes of care regarding cystitis was similar. No differences were

reported among male chemical and film plant employees. The analysis of these 2000 fluorochemical medical surveillance data showed no association between the prevalence of abnormal urinalyses and employee serum PFOS levels among the Decatur employees.

Limitations of this study design include its cross-sectional nature which does not adequately allow for the assessment of temporal changes. However, the large participation of employees in 2000 who may have participated in the 1994/95 and/or 1997 fluorochemical medical surveillance programs at these two manufacturing sites has enabled a longitudinal analysis to be performed. This longitudinal analysis is the focus of a separate 3M investigation (Olsen et al, 2001a). Although still very limited in numbers, we were able to provide separate cross-sectional analyses for female employees, for the first time, which showed no biologically relevant associations between serum PFOS and/or PFOA levels with clinical chemistries, thyroid hormones or hematology results. Because 3M has announced a phase-out of the production of perfluorooctanyl chemistry-related materials, we anticipate that the Antwerp and Decatur employee population mean PFOS and PFOA serum levels should be lower when measured during the next fluorochemical medical surveillance program. These future analyses may be hindered by the fewer employees in the workforce as a consequence of the phase-out announced by the company. Another study limitation was the lower serum PFOS and PFOA levels measured among these employees compared with those suspected to cause effects in laboratory animals.

In summary, the findings from the 2000 fluorochemical medical surveillance program continue to suggest that Antwerp and Decatur fluorochemical production and non-production employees do not show substantial changes in serum hepatic enzymes,

cholesterol, or lipoproteins associated with the serum PFOS and PFOA levels measured.

A separate longitudinal analysis is reported for the fluorochemical medical surveillance

Antwerp and Decatur program data from 1994 through 2000.

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# REFERENCES

3M Company (2000). SIDS Initial assessment repot: Perfluorooctane sulfonic acid and its salts. St. Paul (MN):3M Company, (unpublished report).

Alexander BH (2001a). Mortality study of workers employed at the 3M Cottage Grove facility. Minneapolis (MN):University of Minnesota, (unpublished report).

Alexander BH (2001b). Mortality study of workers employed at the 3M Decatur facility. Minneapolis (MN):University of Minnesota, (unpublished report).

Butenhoff JL, Costa G, Elcombe C, Farrar D, Hansen K, Iwai H, Jung R, Kennedy G, Lieder P, Olsen GW, Thomford P. Toxicity of ammonium perfluorooctanoate (APFO) in cynomolgus monkeys after 26 weeks of oral dosing. St. Paul (MN):3M Company, (unpublished report)

Gilliland FD, Mandel JS (1993). Mortality among employees of a perfluorooctanoic acid production plant. J Occup Med 35:950-954.

Gilliland FD, Mandel JS (1996). Serum perfluorooctanoic acid and hepatic enzymes, lipoproteins and cholesterol: a study of occupationally exposed men. Am J Ind Med 129:560-568.

Hansen KJ, Clemen LA, Ellefson ME, Johnson JHO (2001). Compound-specific, quantitative characterization of organic fluorochemicals in biological matrices. Environ Sci Technol 35:766-770.

Haughom B, Spydevold O (1992). The mechanism underlying the hypolipemic effect of perfluooctanoic acid (PFOA), perfluoroctanesulphonic acid (PFOSA) and clofibric acid. Biochemica et Biophysica Acta 1128:65-72.

Ikeda T, Fukuda K, Mori I, Enomoto M, Komai T, Suga T (1987). Induction of cytochrome P-450 and peroixome proliferation in rat liver by perfluorinated octanesulfonic acid. In: *Perixosmes in Biology and Medicine.* (HD Fahmi and H Sies, eds) New York:Springer Verlag, pp 304-308.

Olsen GW. Burris JM, Mandel JH, Zobel LR (1998a). An epidemiologic investigation of clinical chemistries, hematology and hormones in relation to serum levels of perfluorooctane sulfonate in male fluorochemical production employees. St. Paul:3M Company (unpublished report).

Olsen GW, Gilliland FD, Burlew MM, Burris JM, Mandel JS, Mandel JH (1998b). An epidemiologic investigation of reproductive hormones in men with occupational exposure to perfluorooctanoic acid. JOEM (40(7):614-621.

Olsen GW, Burris JM, Mandel JH, Zobel LR (1999a). Serum perfluorooctane sulfonate and hepatic and lipid clinical chemistry tests in fluorochemical production employees. JOEM 41(9):799-806.

Olsen GW, Logan PW, Simpson CA, Hansen KJ, Burris JM, Burlew MM, Schumpert JC, Mandel JH (1999b). Fluorochemical exposure assessment of Decatur chemical and film plant employees. St. Paul:3M Company (unpublished report).

Olsen GW, Burris JM, Burlew MM, Mandel JH (2000). Plasma cholecystokinn and hepatic enzymes, cholesterol and lipoproteins in ammonium perfluorooctanoate production workers. Drug Chem Toxicol 23(4):603-620.

Olsen GW, Burlew MM, Burris JB, Mandel JM (2001a). A longitudinal analysis of serum perlfuorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) levels in relation to lipid and clinical chemistry test results from male employee participants of the 1994/95, 1997 and 2000 fluorochemical medical surveillance program. St. Paul, MN:3M Company (unpublished report).

Olsen GW, Schmickler MN, Tierens JM, Logan PW, Burris JM, Burlew MM, Lundberg JK. Mandel JH (2001b). Descriptive summary of serum fluorochemical levels among employee participants of the year 2000 Antwerp fluorochemical medical surveillance program. St. Paul:3M Company (unpublished report).

Olsen GW, Logan PW, Simpson CA, Burris JM, Burlew MM, Lundberg JK, Mandel JH (2001c). Descriptive summary of serum fluorochemical levels among employee participants of the year 2000 Decatur fluorochemical medical surveillance program. St Paul:3M Company (unpublished report).

Olsen GW. Burlew MM, Hocking BB, Skratt JC, Burris JM, Mandel JH (2001d). An epidemiologic analysis of episodes of care of 3M Decatur chemical and film plant employees. 1993-1998. St. Paul MN:3M Company (unpublished report).

Pastoor TP, Lee KP, Perri MA, Gillies PJ (1987). Biochemical and morphological studies of ammonium perfluorooctnoate-induced hepatomegaly and peroxisome proliferation. Exp Mol Pathol 47:98-109.

SAS Institute, Inc. (1990). SAS Users Guide:Statistics Version 6. Cary, NC:SAS Institute Inc.

Seacat AM, Thomford PJ, Hansen KJ, Clemen LA, Case MT, Butenhoff JL (2001a). Sub-chronic dietary toxicity of potassium perfluorooctanesulfonic acid in rats. Toxicol Sci (submitted 2001a).

Seacat AM, Thoford PJ, Hansen KJ, Olsen GW, Case MT, Butenhoff JL. Subchronic toxicity studies on perfluorooctanesulfonate potassium salt in cynomolgus monkeys. Toxicol Sci (submitted. 2001b).

Sohlenius AK, Eriksson AM, Hogstrom C, Kimland M, DePierre JW (1993). Perfluorooctane sulfonic acid is a potent inducer of peroxisomal fatty acid B-oxidation and other activities known to be affected by peroxisome proliferators in mouse liver. Pharmacol Toxicol 72:90-93.

Table 1

Number of Employee Participants in the 2000 Antwerp and Decatur Medical Surveillance Programs

| | Antwerp (N = 255) | | | | Decatur (N = 263) | | | |
| | Male (N = 206) | | Female (N = 49) | | Male (N = 215) | | Female (N = 48) | |
| | Production | Non-Production | Production | Non-Production | Production | Non-Production | Production | Non-Production |
|---|---|---|---|---|---|---|---|---|
| | 150 (73)* | 56 (27)* | 6 (12)* | 43 (88)* | 161 (75)* | 54 (25)* | 30 (63)* | 18 (37)* |

*Percent in parenthesis

Table 2

Mean Value for Male Employee Participants' Serum Fluorochemical Levels,
Demographics, Clinical Chemistries and Thyroid Results

| | All | | Production | | Non-Production | |
|---|---|---|---|---|---|---|
| | Antwerp (N = 206) | Decatur (N = 215) | Antwerp (N = 150) | Decatur (N = 161) | Antwerp (N = 56) | Decatur (N = 54) |
| PFOS | 0.96[d] | 1.40 | 1.16[c] | 1.63 | 0.42[b] | 0.73 |
| PFOA | 1.03[d] | 1.90 | 1.28[d] | 2.34 | 0.34[b] | 0.59 |
| TOF | 1.60[d] | 2.65 | 1.97[d] | 3.18 | 0.61[b] | 1.07 |
| Age | 37[d] | 43 | 36[d] | 42 | 40[b] | 45 |
| BMI | 24.8[d] | 28.8 | 24.6[d] | 28.9 | 25.2[d] | 28.4 |
| Years Worked | 13[c] | 16 | 12[a] | 15 | 15[c] | 22 |
| Cigarettes/day | 4 | 6 | 5 | 6 | 2 | 5 |
| Drinks/day | 1.1[d] | 0.1 | 1.1[d] | 0.1 | 1.1[d] | 0.2 |
| Cholesterol | 218 | 215 | 215 | 217 | 225[a] | 209 |
| HDL | 55[d] | 44 | 55[d] | 43 | 55[c] | 45 |
| Triglycerides | 124[d] | 191 | 124[d] | 198 | 122[b] | 169 |
| Alk Phos | 60[d] | 74 | 60[d] | 76 | 60[a] | 67 |
| GGT | 23[d] | 31 | 23[d] | 31 | 26[b] | 29 |
| AST | 23[c] | 26 | 23[d] | 26 | 24 | 25 |
| ALT | 23[d] | 35 | 22[d] | 36 | 25 | 31 |

Table 2 (continued)

| | | | | | | |
|---|---|---|---|---|---|---|
| Total Bilirubin | 1.0[d] | 0.7 | 1.0[d] | 0.7 | 1.1[d] | 0.8 |
| Direct Bilirubin | 0.1[c] | 0.1 | 0.1[b] | 0.1 | 0.1 | 0.1 |
| BUN | 19[d] | 15 | 19[d] | 15 | 19[d] | 15 |
| Creatinine | 1.2 | 1.1 | 1.1[d] | 1.2 | 1.2 | 1.1 |
| Glucose | 85[d] | 95 | 84[d] | 95 | 87[a] | 94 |
| TSH | 2.0[a] | 2.9 | 2.0[a] | 3.1 | 1.9 | 2.2 |
| T4 | 8.2 | 8.4 | 8.3 | 8.4 | 8.1 | 8.5 |
| Free T4 | 1.1[c] | 1.1 | 1.1[c] | 1.1 | 1.1 | 1.1 |
| T3 | 131[b] | 125 | 132[a] | 127 | 126 | 120 |
| THBR | 34[d] | 31 | 34[d] | 30 | 35[d] | 31 |
| FTI | 2.7[d] | 2.5 | 2.7[d] | 2.5 | 2.7[a] | 2.5 |

[a] p < .05 compared to Decatur (t test)
[b] p < .01 compared to Decatur (t test)
[c] p < .001 compared to Decatur (t test)
[d] p < .0001 compared to Decatur (t test)

000163

Table 3

Mean Values for Female Employee Participants' Serum Fluorochemical Levels,
Demographics, Clinical Chemistries and Thyroid Results

|  | Antwerp (N = 49) | Decatur (N = 48) |
|---|---|---|
| PFOS | 0.13[d] | 0.93 |
| PFOA | 0.07[d] | 1.23 |
| TOF | 0.17[d] | 1.76 |
| Age | 36 | 42 |
| BMI | 22.8[d] | 27.7 |
| Years Worked | 12[a] | 13 |
| Cigarettes/day | 2[d] | 5 |
| Drinks/day | 0.5[d] | 0.1 |
| Cholesterol | 208 | 200 |
| HDL | 68[a] | 59 |
| Triglycerides | 94[d] | 133 |
| Alk Phos | 46[a] | 65 |
| GGT | 12[d] | 18 |
| AST | 18 | 20 |
| ALT | 13[d] | 19 |
| Total Bilirubin | 0.8[b] | 0.6 |
| Direct Bilirubin | 0.1 | 0.1 |
| BUN | 16 | 12 |
| Creatinine | 0.9 | 0.8 |
| Glucose | 85 | 87 |
| TSH | 2.3 | 2.3 |
| T4 | 10.2 | 9.3 |
| Free T4 | 1.1[b] | 1.0 |
| T3 | 148[b] | 128 |
| THBR | 30[a] | 28 |
| FTI | 2.9[d] | 2.5 |

[a] $p < .05$ compared to Decatur (student t test)
[b] $p < .01$ compared to Decatur (student t test)
[c] $p < .001$ compared to Decatur (student t test)
[d] $p < .0001$ compared to Decatur (student t test)

## Table 4

### Antwerp Male Production Employee (N = 150)

Fluorochemical, Demographic and Clinical Chemistry Results by Quartile of Serum PFOS Distribution

| | Quartile 1 (N = 37) | | | | Quartile 2 (N = 38) | | | | Quartile 3 (N = 38) | | | | Quartile 4 (N = 37) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| PFOS | 0.29[3,4] | 0.33 | 0.11 | 0.04 – 0.41 | 0.58[3,4] | 0.57 | 0.12 | 0.41 – 0.78 | 1.18[1,2,4] | 1.16 | 0.22 | 0.79 – 1.66 | 2.61[1,2,3] | 2.27 | 1.06 | 1.67 – 6.24 |
| PFOA | 0.94[4] | 0.42 | 1.06 | 0.02 – 4.03 | 1.51 | 0.72 | 1.70 | 0.07 – 7.04 | 1.02 | 1.00 | 0.60 | 0.21 – 3.27 | 1.66[1] | 1.64 | 0.81 | 0.25 – 3.59 |
| TOF | 0.92[2,3,4] | 0.60 | 0.78 | 0.05 – 3.03 | 1.63[1,4] | 1.08 | 1.26 | 0.42 – 5.69 | 1.82[1,4] | 1.80 | 0.55 | 1.03 – 3.14 | 3.51[1,2,3] | 3.30 | 1.18 | 1.92 – 7.36 |
| Age | 33[4] | 34 | 7 | 23 – 48 | 37 | 36 | 9 | 21 – 56 | 37 | 36 | 9 | 22 – 55 | 39[1] | 39 | 8 | 28 – 55 |
| BMI | 24.3 | 23.8 | 2.7 | 19.2 – 33.2 | 24.9 | 24.3 | 3.1 | 19.0 – 34.7 | 25.0 | 25.3 | 2.8 | 17.5 – 32.3 | 24.3 | 24.7 | 3.0 | 17.8 – 30.9 |
| Years Worked | 8[2,3,4] | 5 | 6 | 2 – 25 | 12[1] | 11 | 9 | 2 – 29 | 12[1] | 13 | 7 | 1 – 29 | 15[1] | 15 | 6 | 5 – 29 |
| Cigarettes/day | 5 | 0 | 7 | 0 – 20 | 5 | 0 | 8 | 0 – 25 | 4 | 0 | 6 | 0 – 20 | 7 | 0 | 8 | 0 – 25 |
| Drinks/day | 1.2 | 1.0 | 1 | 0 – 4 | 1.1 | 0.9 | 1.0 | 0 – 4 | 0.9 | 0.7 | 0.9 | 0 – 4 | 1.1 | 0.7 | 1.2 | 0 – 5 |
| Cholesterol | 207 | 202 | 39 | 145 – 308 | 216 | 217 | 41 | 148 – 295 | 212 | 196 | 41 | 105 – 297 | 226 | 232 | 46 | 122 – 316 |
| HDL | 57 | 57 | 13 | 32 – 85 | 52 | 49 | 10 | 38 – 72 | 54 | 53 | 12 | 29 – 80 | 57 | 51 | 19 | 26 – 119 |
| Triglycerides | 102 | 102 | 49 | 34 – 221 | 125 | 113 | 87 | 35 – 546 | 140 | 113 | 124 | 41 – 731 | 130 | 105 | 75 | 42 – 346 |
| Alk Phos | 60 | 61 | 15 | 34 – 96 | 60 | 60 | 15 | 30 – 113 | 59 | 59 | 15 | 30 – 94 | 61 | 62 | 14 | 21 – 89 |
| GGT | 20 | 16 | 11 | 8 – 53 | 24 | 20 | 16 | 8 – 89 | 21 | 19 | 11 | 10 – 64 | 26 | 19 | 19 | 7 – 85 |
| AST | 24 | 24 | 8 | 13 – 58 | 24 | 23 | 5 | 16 – 41 | 22 | 21 | 5 | 13 – 33 | 23 | 22 | 6 | 15 – 39 |
| ALT | 23 | 22 | 10 | 11 – 71 | 22 | 21 | 8 | 10 – 43 | 22 | 20 | 9 | 9 – 46 | 20 | 20 | 9 | 8 – 45 |
| Total Bilirubin | 1.0 | 1.0 | 0.3 | 0.6 – 1.6 | 1.0 | 0.9 | 0.4 | 0.5 – 2.0 | 1.0 | 1.0 | 0.3 | 0.5 – 2.3 | 1.0 | 0.9 | 0.3 | 0.4 – 2.2 |
| Direct Bilirubin | 0.1 | 0.1 | 0.04 | 0.0 – 0.2 | 0.1 | 0.1 | 0.1 | 0.0 – 0.3 | 0.1 | 0.1 | 0.03 | 0.0 – 0.2 | 0.1 | 0.1 | 0.1 | 0.0 – 0.4 |
| BUN | 18[3] | 17 | 4 | 11 – 25 | 18 | 18 | 4 | 12 – 25 | 20[1] | 19 | 5 | 14 – 31 | 19 | 19 | 4 | 11 – 30 |
| Creatinine | 1.1 | 1.1 | 0.2 | 0.9 – 1.5 | 1.1 | 1.1 | 0.2 | 0.8 – 1.7 | 1.1 | 1.1 | 0.2 | 0.8 – 2.0 | 1.1 | 1.0 | 0.2 | 0.8 – 1.5 |
| Glucose | 85 | 87 | 19 | 31 – 131 | 86 | 88 | 16 | 49 – 113 | 84 | 85 | 21 | 45 – 168 | 80 | 83 | 20 | 40 – 120 |

[1] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 1st quartile
[2] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 2nd quartile
[3] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 3rd quartile

Table 5

Antwerp Male Production Employee (N = 150)
Thyroid Results* by Quartile of Serum PFOS Distribution**

| | Quartile 1 (N = 37) | | | | Quartile 2 (N = 38) | | | | Quartile 3 (N = 38) | | | | Quartile 4 (N = 37) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| TSH | 1.8 | 1.6 | 1.1 | 05 – 5.7 | 2.0 | 2.0 | 0.9 | 0.7 – 5.5 | 2.0 | 1.7 | 1.1 | 0.8 – 6.1 | 2.2 | 1.6 | 3.0 | 0.5 – 19.4 |
| T4 | 8.2 | 8.3 | 1.5 | 5.4 – 11.5 | 8.5 | 8.6 | 1.4 | 6.6 – 12.0 | 8.2 | 8.1 | 1.4 | 5.0 – 11.5 | 8.1 | 8.2 | 1.4 | 4.7 – 11.0 |
| Free T4 | 1.2 | 1.1 | 0.2 | 0.9 – 1.5 | 1.1 | 1.1 | 0.1 | 0.9 – 1.4 | 1.1 | 1.1 | 0.2 | 0.6 – 1.6 | 1.1 | 1.1 | 0.2 | 0.8 – 1.6 |
| T3 | 127 | 127 | 15 | 95 – 155 | 134 | 132 | 17 | 102 – 169 | 132 | 132 | 19 | 97 – 180 | 136 | 137 | 22 | 98 – 185 |
| THBR | 34 | 34 | 3 | 28 – 40 | 34 | 34 | 2 | 29 – 39 | 34 | 34 | 3 | 29 – 43 | 34 | 34 | 2 | 29 – 41 |
| FTI | 2.8 | 2.6 | 0.5 | 2.1 – 4.2 | 2.8 | 2.8 | 0.4 | 2.1 – 4.0 | 2.7 | 2.7 | 0.4 | 1.9 – 3.9 | 2.7 | 2.7 | 0.4 | 1.6 – 3.6 |

*No significantly different (P < .05, Bonferroni (Dunn) t test) mean values
**See Table 4 for serum PFOS quartile distribution

Table 6

Antwerp Male Production Employee (N = 150)
Hematology Results* by Quartile of Serum PFOS Distribution**

| | Quartile 1 (N = 37) | | | | Quartile 2 (N = 38) | | | | Quartile 3 (N = 37) | | | | Quartile 4 (N = 37) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| HCT | 46 | 46 | 3 | 41 – 53 | 46 | 46 | 3 | 39 – 51 | 46 | 46 | 3 | 40 – 51 | 46 | 46 | 3 | 41 – 51 |
| HGB | 15.5 | 15.4 | 0.8 | 14.0 – 17.4 | 15.5 | 15.5 | 0.9 | 13.2 – 18.1 | 15.4 | 15.5 | 0.8 | 13.6 – 17.3 | 15.3 | 15.3 | 0.9 | 13.4 – 17.1 |
| RBC | 5.2 | 5.2 | 0.3 | 4.6 – 5.9 | 5.1 | 5.2 | 0.3 | 4.4 – 5.9 | 5.1 | 5.1 | 0.3 | 4.7 – 5.9 | 5.0 | 5.0 | 0.3 | 4.0 – 5.8 |
| WBC | 7.0 | 6.4 | 1.8 | 4.2 – 11.4 | 7.3 | 7.1 | 1.8 | 4.4 – 11.5 | 7.6 | 7.4 | 1.6 | 5.2 – 11.1 | 7.2 | 6.9 | 2.1 | 4.5 – 15.6 |
| Platelets | 244 | 242 | 57 | 138 – 380 | 254 | 250 | 51 | 167 – 373 | 253 | 242 | 73 | 106 – 427 | 249 | 247 | 55 | 137 - 369 |

*No significantly different (P < .05, Bonferroni (Dunn) t test) mean values
**See Table 4 for serum PFOS quartile distribution

Table 7

Antwerp Male Non-Production Employee (N = 56)

Fluorochemical, Demographic and Clinical Chemistry Results by Quartile of Serum PFOS Distribution

| | Quartile 1 (N = 14) | | | | Quartile 2 (N = 13) | | | | Quartile 3 (N = 15) | | | | Quartile 4 (N = 14) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| PFOS | 0.13[3,4] | 0.13 | 0.05 | 0.05 – 0.20 | 0.27[4] | 0.28 | 0.03 | 0.21 – 0.31 | 0.40[1,4] | 0.41 | 0.05 | 0.32 – 0.48 | 0.90[1,2,3] | 0.64 | 0.47 | 0.49 – 1.76 |
| PFOA | 0.18[4] | 0.06 | 0.46 | 0.01 – 1.78 | 0.19[4] | 0.15 | 0.13 | 0.05 – 0.51 | 0.37 | 0.32 | 0.23 | 0.06 – 0.85 | 0.62[1,2] | 0.42 | 0.49 | 0.12 – 1.78 |
| TOF | 0.24[3,4] | 0.17 | 0.34 | 0.06 – 1.38 | 0.37[4] | 0.35 | 0.11 | 0.22 – 0.64 | 0.60[4] | 0.54 | 0.19 | 0.37 – 0.96 | 1.22[1,2,3] | 1.09 | 0.69 | 0.56 – 3.01 |
| Age | 40 | 36 | 13 | 23 – 58 | 41 | 42 | 6 | 31 – 53 | 38 | 40 | 9 | 25 – 56 | 40 | 41 | 9 | 26 – 55 |
| BMI | 24.6 | 25.1 | 3.3 | 19.9 – 31.3 | 25.4 | 24.3 | 3.3 | 21.7 – 34.2 | 26.1 | 25.1 | 3.5 | 21.1 – 33.9 | 24.4 | 24.2 | 3.0 | 20.4 – 30.1 |
| Years Worked | 15 | 15 | 10 | 1 – 29 | 17 | 16 | 6 | 6 – 29 | 13 | 13 | 8 | 3 – 26 | 15 | 15 | 9 | 2 – 27 |
| Cigarettes/day | 1 | 0 | 5 | 0 – 20 | 0 | 0 | 0 | 0 – 0 | 4 | 0 | 7 | 0 – 20 | 2 | 0 | 4 | 0 – 10 |
| Drinks/day | 1.1 | 0.7 | 0.9 | 0.1 – 2.9 | 1.0 | 0.7 | 1.3 | 0.0 – 5.0 | 1.1 | 1.1 | 0.9 | 0.1 – 3.4 | 1.3 | 0.9 | 1.6 | 0.0 – 6.4 |
| Cholesterol | 215 | 218 | 37 | 140 – 293 | 244 | 231 | 43 | 191 – 331 | 219 | 223 | 39 | 157 – 277 | 225 | 231 | 33 | 178 – 277 |
| HDL | 55 | 54 | 11 | 40 – 78 | 61 | 58 | 27 | 31 – 121 | 53 | 49 | 10 | 40 – 77 | 54 | 57 | 18 | 31 – 100 |
| Triglycerides | 94 | 78 | 39 | 45 – 177 | 159 | 118 | 129 | 36 – 463 | 120 | 99 | 61 | 49 – 254 | 117 | 95 | 72 | 37 – 262 |
| Alk Phos | 59 | 59 | 17 | 30 – 91 | 62 | 63 | 11 | 43 – 80 | 61 | 61 | 18 | 30 – 94 | 57 | 56 | 12 | 39 – 77 |
| GGT | 20 | 18 | 14 | 8 – 65 | 32 | 21 | 26 | 13 – 111 | 26 | 16 | 21 | 7 – 80 | 25 | 16 | 26 | 6 – 107 |
| AST | 24 | 22 | 7 | 15 – 37 | 25 | 23 | 8 | 15 – 44 | 25 | 22 | 7 | 14 – 38 | 24 | 23 | 8 | 16 – 49 |
| ALT | 24 | 21 | 10 | 12 – 41 | 27 | 25 | 14 | 10 – 61 | 24 | 21 | 11 | 11 – 46 | 24 | 21 | 11 | 12 – 44 |
| Total Bilirubin | 1.2 | 1.2 | 0.3 | 0.5 – 1.9 | 1.2 | 1.2 | 0.4 | 0.8 – 2.0 | 0.9 | 0.9 | 0.3 | 0.5 – 1.7 | 1.1 | 1.0 | 0.3 | 0.7 – 1.9 |
| Direct Bilirubin | 0.1 | 0.1 | 0.04 | 0.1 – 0.2 | 0.1 | 0.1 | 0.04 | 0.1 – 0.2 | 0.1 | 0.1 | 0.1 | 0.0 – 0.3 | 0.1 | 0.1 | 0.03 | 0.1 – 0.2 |
| BUN | 18 | 18 | 4 | 15 – 27 | 22 | 19 | 15 | 14 – 71 | 18 | 18 | 4 | 13 – 25 | 19 | 19 | 3 | 14 – 24 |
| Creatinine | 1.2 | 1.2 | 0.2 | 1.0 – 1.7 | 1.5 | 1.1 | 1.3 | 0.9 – 5.8 | 1.2 | 1.2 | 0.2 | 0.8 – 1.5 | 1.1 | 1.1 | 0.2 | 0.8 – 1.6 |
| Glucose | 84 | 86 | 14 | 60 – 104 | 88 | 92 | 15 | 50 – 107 | 87 | 95 | 20 | 48 – 114 | 91 | 90 | 14 | 68 – 115 |

[1] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 1st quartile
[2] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 2nd quartile
[3] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 3rd quartile

; Table 8

Antwerp Male Non-Production Employees (N = 56)
Thyroid Results* by Quartile of Serum PFOS Distribution**

| | Quartile 1 (N = 14) | | | | Quartile 2 (N = 13) | | | | Quartile 3 (N = 15) | | | | Quartile 4 (N = 14) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| TSH | 2.1 | 2.0 | 1.1 | 0.4 – 4.2 | 2.0 | 1.9 | 1.2 | 0.7 – 5.4 | 1.6 | 1.7 | 1.0 | 0.03 – 4.3 | 2.0 | 1.6 | 1.4 | 1.0 – 6.1 |
| T4 | 8.9 | 8.9 | 1.1 | 6.8 – 10.4 | 7.8 | 8.6 | 1.5 | 5.0 – 9.4 | 7.9 | 7.7 | 1.3 | 5.7 – 9.8 | 7.9 | 7.7 | 1.9 | 4.2 – 11.4 |
| Free T4 | 1.2 | 1.2 | 0.2 | 1.0 – 1.5 | 1.1 | 1.2 | 0.2 | 0.9 – 1.5 | 1.1 | 1.1 | 0.2 | 0.9 – 1.5 | 1.1 | 1.2 | 0.2 | 0.9 – 1.4 |
| T3 | 131 | 128 | 16 | 106 – 164 | 120 | 118 | 12 | 103 – 145 | 128 | 126 | 25 | 91 – 161 | 125 | 129 | 18 | 87 – 147 |
| THBR | 33 | 34 | 2 | 30 - 36 | 35 | 33 | 4 | 30 – 42 | 35 | 34 | 3 | 28 – 41 | 35 | 34 | 2 | 32 – 41 |
| FTI | 2.9 | 3.0 | 0.3 | 2.3 – 3.4 | 2.6 | 2.7 | 0.4 | 2.0 – 3.4 | 2.7 | 2.7 | 0.4 | 2.1 – 3.5 | 2.7 | 2.7 | 0.6 | 1.7 – 3.7 |

*No significantly different (P < .05, Bonferroni (Dunn) t test) mean values
**See Table 7 for serum PFOS quartile distribution

Table 9

Antwerp Male Production Employee (N = 49)
Hematology Results* by Quartile of Serum PFOS Distribution**

| | Quartile 1 (N = 14) | | | | Quartile 2 (N = 13) | | | | Quartile 3 (N = 15) | | | | Quartile 4 (N = 14) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| HCT | 44 | 44 | 2 | 40 – 48 | 47 | 47 | 2 | 42 – 49 | 46 | 46 | 3 | 42 – 51 | 45 | 45 | 2 | 41 – 50 |
| HGB | 15.1 | 15.0 | 1.1 | 12.2 – 17.0 | 15.6 | 15.5 | 0.7 | 14.3 – 16.5 | 15.4 | 15.3 | 0.8 | 14.0 – 17.0 | 15.3 | 15.3 | 0.8 | 14.1 – 17.1 |
| RBC | 5.1 | 5.1 | 0.2 | 4.8 – 5.6 | 5.1 | 5.1 | 0.3 | 4.6 – 5.6 | 5.1 | 5.1 | 0.3 | 4.5 – 5.7 | 5.0 | 5.0 | 0.3 | 4.7 – 5.5 |
| WBC | 6.6 | 6.4 | 1.3 | 5.1 – 10.1 | 6.9 | 6.5 | 1.7 | 4.7 – 10.7 | 6.5 | 6.0 | 2.1 | 3.8 – 11.0 | 6.5 | 6.4 | 1.3 | 4.9 – 9.6 |
| Platelets | 228 | 226 | 23 | 183 – 258 | 267 | 270 | 49 | 206 – 353 | 225 | 221 | 53 | 129 – 335 | 234 | 234 | 39 | 172 – 306 |

*No significantly different (P < .05, Bonferroni (Dunn) t test) mean values
**See Table 7 for serum PFOS quartile distribution

## Table 10

### Antwerp Female Production* and Non-Production Employee (N = 49)
### Fluorochemical, Demographic and Clinical Chemistry Results by Quartile of Serum PFOS

| | Quartile 1 (N = 12) | | | | Quartile 2 (N = 12) | | | | Quartile 3 (N = 13) | | | | Quartile 4 (N = 12) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| PFOS | 0.06 | 0.06 | 0.01 | 0.04 – 0.08 | 0.09 | 0.09 | 0.01 | 0.08 – 0.10 | 0.11 | 0.11 | 0.01 | 0.10 – 0.14 | 0.26[1,2,3] | 0.21 | 0.13 | 0.15 – 0.55 |
| PFOA | 0.03 | 0.02 | 0.02 | 0.01 – 0.08 | 0.03 | 0.02 | 0.01 | 0.01 – 0.06 | 0.04 | 0.03 | 0.01 | 0.02 – 0.07 | 0.20[2] | 0.09 | 0.31 | 0.02 – 1.11 |
| TOF | 0.08 | 0.07 | 0.02 | 0.05 – 0.12 | 0.09 | 0.09 | 0.01 | 0.07 – 0.11 | 0.12 | 0.11 | 0.02 | 0.09 – 0.15 | 0.40[1,2,3] | 0.26 | 0.34 | 0.13 – 1.25 |
| Age | 32 | 31 | 8 | 24 – 50 | 36 | 34 | 9 | 24 – 52 | 38 | 36 | 5 | 31 – 48 | 37 | 36 | 6 | 29 – 52 |
| BMI | 23.8 | 23.5 | 2.6 | 18.8 – 28.3 | 21.9 | 21.8 | 2.5 | 18.4 – 26.3 | 23.7 | 21.3 | 4.6 | 17.3 – 32.3 | 21.8 | 22.0 | 1.7 | 18.3 – 25.0 |
| Years Worked | 7[3] | 5 | 7 | 0.8 – 22 | 13 | 12 | 8 | 4 – 29 | 15[1] | 14 | 6 | 9 – 28 | 13 | 13 | 7 | 5 – 29 |
| Cigarettes/day | 1 | 0 | 3 | 0 – 10 | 2 | 0 | 6 | 0 – 20 | 2 | 0 | 5 | 0 – 15 | 2 | 0 | 4 | 0 – 13 |
| Drinks/day | 0.2[2,3] | 0.1 | 0.3 | 0 – 1.0 | 0.6 | 0.5 | 0.4 | 0.1 – 1.3 | 0.6[1] | 0.4 | 0.4 | 0.0 – 1.4 | 0.6 | 0.5 | 0.5 | 0.1 – 1.6 |
| Cholesterol | 205 | 195 | 30 | 155 – 253 | 214 | 224 | 45 | 132 – 274 | 208 | 197 | 39 | 160 – 302 | 207 | 197 | 32 | 164 – 271 |
| HDL | 62 | 60 | 11 | 46 – 85 | 71 | 72 | 19 | 46 – 121 | 68 | 64 | 18 | 43 – 104 | 72 | 67 | 16 | 53 – 104 |
| Triglycerides | 111 | 99 | 57 | 46 – 248 | 73 | 80 | 27 | 26 – 112 | 98 | 93 | 43 | 46 – 172 | 94 | 87 | 44 | 32 – 171 |
| Alk Phos | 53 | 54 | 14 | 22 – 70 | 44 | 48 | 14 | 25 – 61 | 44 | 45 | 10 | 26 – 61 | 42 | 42 | 11 | 20 – 59 |
| AST | 21 | 20 | 5 | 14 – 31 | 17 | 17 | 5 | 11 – 27 | 18 | 17 | 6 | 9 – 26 | 17 | 15 | 6 | 12 – 33 |
| ALT | 14 | 12 | 7 | 8 – 35 | 12 | 12 | 2 | 8 – 17 | 15 | 13 | 7 | 6 – 34 | 11 | 11 | 3 | 7 – 18 |
| GGT | 12 | 10 | 8 | 3 – 32 | 11 | 11 | 5 | 2 – 19 | 14 | 10 | 10 | 7 – 41 | 10 | 10 | 4 | 5 – 23 |
| Total Bilirubin | 0.8 | 0.7 | 0.2 | 0.5 – 1.2 | 1.0 | 1.0 | 0.3 | 0.5 – 1.7 | 0.8 | 0.8 | 0.3 | 0.3 – 1.3 | 0.7 | 0.7 | 0.2 | 0.3 – 1.2 |
| Direct Bilirubin | 0.1 | 0.1 | 0.07 | 0.0 – 0.2 | 0.1 | 0.1 | 0.09 | 0.1 – 0.4 | 0.1 | 0.1 | 0.06 | 0.0 – 0.2 | 0.1 | 0.1 | 0.0 | 0.1 – 0.1 |
| BUN | 12[3,4] | 12 | 2 | 9 – 16 | 15 | 15 | 3 | 11 – 23 | 18[1] | 19 | 4 | 9 – 22 | 16[1] | 16 | 3 | 13 – 23 |
| Creatinine | 0.9 | 0.9 | 0.2 | 0.6 – 1.1 | 0.9 | 0.9 | 0.2 | 0.7 – 1.3 | 1.0 | 1.0 | 0.2 | 0.7 – 1.4 | 1.0 | 1.0 | 0.1 | 0.8 – 1.2 |
| Glucose | 75 | 76 | 16 | 38 – 98 | 86 | 90 | 12 | 65 – 101 | 89 | 91 | 11 | 65 – 105 | 88 | 90 | 17 | 49 – 117 |

*Number of Female employees by production category by quartile

| | Q1 | Q2 | Q3 | Q4 |
|---|---|---|---|---|
| Production | 3 | 1 | 0 | 2 |
| Non-Production | 9 | 11 | 13 | 10 |

[1] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 1st quartile
[2] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 2nd quartile
[3] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 3rd quartile
[4] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 4th quartile

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## Table 11

### Antwerp Female Production and Non-Production Employee (N = 49)
### Thyroid Results* by Quartile of Serum PFOS Distribution**

| | Quartile 1 (N = 12) | | | | Quartile 2 (N = 12) | | | | Quartile 3 (N = 13) | | | | Quartile 4 (N = 12) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| TSH | 2.0 | 1.9 | 1.4 | 0.03 – 4.9 | 2.4 | 2.4 | 1.0 | 0.6 – 4.1 | 2.2 | 1.8 | 1.8 | 0.03 – 6.7 | 2.6 | 2.0 | 1.6 | 1.0 – 6.5 |
| T4 | 10.7 | 11.3 | 2.2 | 6.6 – 13.8 | 9.7 | 9.7 | 1.8 | 6.9 – 12.3 | 10.5 | 10.7 | 3.6 | 4.6 – 18.3 | 10.0 | 9.8 | 2.3 | 6.7 – 13.3 |
| Free T4 | 1.1 | 1.1 | 0.1 | 0.8 – 1.3 | 1.1 | 1.2 | 0.1 | 0.9 – 1.3 | 1.4 | 1.1 | 1.0 | 0.7 – 4.6 | 1.0 | 1.0 | 0.1 | 0.9 – 1.2 |
| T3 | 157 | 164 | 29 | 106 – 191 | 128 | 134 | 22 | 98 – 163 | 159 | 145 | 66 | 81 – 345 | 144 | 135 | 34 | 109 – 228 |
| THBR | 27 | 27 | 5 | 19 – 34 | 31 | 31 | 4 | 25 – 36 | 31 | 32 | 7 | 22 – 46 | 29 | 29 | 4 | 24 – 35 |
| FTI | 2.8 | 2.9 | 0.5 | 2.1 – 3.6 | 2.9 | 3.0 | 0.4 | 2.3 – 3.6 | 3.2 | 2.9 | 1.6 | 1.8 – 8.4 | 2.8 | 2.7 | 0.4 | 2.2 – 3.4 |

*No significantly different (P < .05, Bonferroni (Dunn) t test) mean values
**See Table 10 for serum PFOS quartile distribution

Table 12

Antwerp Female Production and Non-Production Employee (N = 49)
Hematology Results* by Quartile of Serum PFOS Distribution**

| | Quartile 1 (N = 12) | | | | Quartile 2 (N = 12) | | | | Quartile 3 (N = 13) | | | | Quartile 4 (N = 12) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| HCT | 40 | 42 | 4 | 29 – 43 | 41 | 41 | 3 | 37 – 45 | 40 | 41 | 2 | 35 – 44 | 41 | 41 | 2 | 38 – 46 |
| HGB | 13.3 | 13.6 | 1.5 | 9.4 – 14.9 | 13.5 | 13.5 | 0.7 | 12.5 – 15.0 | 13.3 | 13.3 | 0.8 | 11.7 – 14.8 | 13.5 | 13.6 | 0.8 | 12.5 – 15.2 |
| RBC | 4.6 | 4.7 | 0.4 | 3.7 – 5.1 | 4.5 | 4.5 | 0.3 | 4.1 – 5.1 | 4.5 | 4.5 | 0.2 | 4.2 – 5.0 | 4.5 | 4.5 | 0.3 | 4.2 – 5.1 |
| WBC | 7.7 | 7.4 | 1.9 | 4.8 – 10.1 | 6.3 | 6.0 | 1.7 | 3.9 – 9.3 | 7.3 | 7.2 | 1.4 | 5.4 – 9.5 | 6.5 | 6.3 | 1.3 | 4.4 – 9.4 |
| Platelets | 261 | 246 | 50 | 189 – 379 | 275 | 282 | 49 | 211 – 374 | 277 | 251 | 68 | 202 – 426 | 269 | 260 | 64 | 181 – 406 |

*No significantly different (P < .05, Bonferroni (Dunn) t test) mean values
**See Table 10 for serum PFOS quartile distribution

## Table 13

### Decatur Male Production Employee (N = 161)

### Fluorochemical, Demographic and Clinical Chemistry Results by Quartile of Serum PFOS Distribution

| | Quartile 1 (N = 40) | | | | Quartile 2 (N = 40) | | | | Quartile 3 (N = 41) | | | | Quartile 4 (N = 40) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| PFOS | 0.55[2,3,4] | 0.55 | 0.16 | 0.11 – 0.75 | 1.01[1,3,4] | 0.99 | 0.18 | 0.76 – 1.30 | 1.74[1,2,4] | 1.74 | 0.28 | 1.32 – 2.29 | 3.22[1,2,3] | 3.03 | 1.22 | 2.31 – 10.06 |
| PFOA | 1.24[3,4] | 1.24 | 0.67 | 0.06 – 2.72 | 1.82[4] | 1.53 | 1.05 | 0.35 – 4.61 | 2.42[1,4] | 2.37 | 1.16 | 0.76 – 7.48 | 3.88[1,2,3] | 3.68 | 1.86 | 1.52 – 12.70 |
| TOF | 1.34[2,3,4] | 1.34 | 0.52 | 0.14 – 2.52 | 2.20[1,3,4] | 2.04 | 0.79 | 0.89 – 4.22 | 3.43[1,2,4] | 3.32 | 1.06 | 1.75 – 6.61 | 5.75[1,2,3] | 5.31 | 1.77 | 3.00 – 12.23 |
| Age | 43 | 44 | 9 | 26 – 63 | 42 | 41 | 9 | 26 – 61 | 42 | 43 | 8 | 28 – 57 | 41 | 41 | 10 | 27 – 60 |
| BMI | 29.0 | 28.1 | 3.7 | 24.5 – 37.6 | 28.4 | 27.3 | 5.2 | 17.2 – 50.1 | 29.9 | 29.2 | 5.0 | 22.6 – 45.5 | 28.3 | 28.3 | 4.0 | 19.9 – 39.2 |
| Years Worked | 12 | 4 | 13 | 2 – 38 | 13 | 5 | 12 | 2 – 34 | 17 | 22 | 12 | 2 – 38 | 16 | 14 | 11 | 3 – 38 |
| Cigarettes/day | 8 | 0 | 13 | 0 – 40 | 5 | 0 | 10 | 0 – 30 | 9 | 0 | 13 | 0 – 40 | 4 | 0 | 9 | 0 – 30 |
| Drinks/day | 0.2 | 0 | 0.3 | 0 – 1 | 0.1 | 0 | 0.2 | 0 – 1 | 0.1 | 0 | 0.2 | 0 – 1 | 0.1 | 0 | 0.2 | 0.0 – 1.0 |
| Cholesterol | 214 | 220 | 43 | 121 – 296 | 224 | 219 | 42 | 155 – 308 | 213 | 208 | 44 | 147 – 384 | 216 | 210 | 39 | 160 – 319 |
| HDL | 42 | 41 | 8 | 29 – 59 | 45 | 44 | 8 | 33 – 75 | 43 | 42 | 11 | 29 – 70 | 43 | 43 | 8 | 28 – 64 |
| Triglycerides | 232 | 198 | 139 | 32 – 633 | 165 | 137 | 101 | 32 – 550 | 202 | 167 | 138 | 44 – 792 | 195 | 175 | 128 | 39 – 796 |
| Alk Phos | 76 | 73 | 20 | 44 – 142 | 74 | 69 | 22 | 39 – 160 | 78 | 75 | 22 | 39 – 139 | 75 | 71 | 20 | 44 – 126 |
| GGT | 33 | 28 | 22 | 7 – 144 | 29 | 23 | 17 | 10 – 87 | 29 | 27 | 13 | 11 – 80 | 34 | 30 | 16 | 10 – 71 |
| AST | 26 | 25 | 7 | 16 – 42 | 26 | 25 | 7 | 15 – 51 | 25 | 24 | 7 | 7 – 39 | 29 | 26 | 11 | 15 – 69 |
| ALT | 33[4] | 31 | 12 | 12 – 63 | 32[4] | 28 | 17 | 6 – 103 | 33[4] | 31 | 12 | 10 – 58 | 44[1,2,3] | 37 | 23 | 12 – 99 |
| Total Bilirubin | 0.7 | 0.7 | 0.2 | 0.3 – 1.5 | 0.8 | 0.8 | 0.2 | 0.4 – 1.2 | 0.7 | 0.7 | 0.2 | 0.4 – 1.1 | 0.7 | 0.7 | 0.2 | 0.4 – 1.3 |
| Direct Bilirubin | 0.1 | 0.1 | 0.1 | 0.0 – 0.2 | 0.1 | 0.1 | 0.1 | 0.0 – 0.7 | 0.1 | 0.1 | .05 | 0.0 – 0.2 | 0.1 | 0.1 | 0.1 | 0.0 – 0.6 |
| BUN | 15 | 15 | 5 | 9 – 33 | 15 | 15 | 4 | 8 – 30 | 15 | 14 | 3 | 8 – 23 | 15 | 15 | 5 | 6 – 26 |
| Creatinine | 1.1 | 1.1 | 0.2 | 0.7 – 1.6 | 1.1 | 1.1 | 0.2 | 0.8 – 1.7 | 1.4 | 1.0 | 2.2 | 0.8 – 15.0 | 1.0 | 1.1 | 0.2 | 0.8 – 1.4 |
| Glucose | 97 | 91 | 19 | 75 – 184 | 93 | 93 | 10 | 75 – 113 | 99 | 93 | 39 | 74 – 381 | 92 | 90 | 12 | 72 – 129 |

[1] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 1st quartile
[2] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 2nd quartile
[3] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 3rd quartile

Table 14

Decatur Male Production Employee (N = 161)
Thyroid Results* by Quartile of Serum PFOS Distribution**

| | Quartile 1 (N = 40) | | | | Quartile 2 (N = 40) | | | | Quartile 3 (N = 41) | | | | Quartile 4 (N = 40) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| TSH | 4.5 | 2.4 | 10.4 | 0.5 – 65.3 | 2.4 | 1.8 | 2.9 | 0.2 – 18.8 | 2.4 | 2.1 | 1.5 | 0.8 – 8.6 | 3.0 | 2.4 | 3.4 | 0.8 – 21.5 |
| T4 | 7.9 | 8.2 | 1.3 | 4.6 – 10.7 | 8.5 | 8.5 | 1.5 | 3.3 – 11.4 | 8.5 | 8.2 | 1.7 | 4.7 – 12.9 | 8.5 | 8.4 | 1.2 | 5.1 – 11.4 |
| Free T4 | 1.0 | 1.0 | 0.1 | 0.6 – 1.3 | 1.1 | 1.1 | 0.2 | 0.4 – 1.4 | 1.1 | 1.1 | 0.2 | 0.7 – 1.5 | 1.1 | 1.0 | 0.1 | 0.8 – 1.3 |
| T3 | 122 | 118 | 19 | 96 – 186 | 124 | 122 | 19 | 93 – 196 | 127 | 119 | 24 | 87 – 172 | 135 | 136 | 23 | 97 – 190 |
| THBR | 31 | 31 | 3 | 24 – 38 | 30 | 30 | 2 | 26 – 37 | 31 | 31 | 3 | 26 – 37 | 30 | 30 | 3 | 25 – 38 |
| FTI | 2.4 | 2.4 | 0.3 | 1.2 – 3.0 | 2.5 | 2.5 | 0.5 | 1.0 – 3.4 | 2.6 | 2.5 | 0.5 | 1.5 – 4.1 | 2.5 | 2.4 | 0.4 | 1.9 – 3.4 |

*No significantly different (P < .05, Bonferroni (Dunn) t test) mean values
**See Table 13 for serum PFOS quartile distribution

Table 15

Decatur Male Production Employee (N = 161)
Hematology Results* by Quartile of Serum PFOS Distribution**

| | Quartile 1 (N = 40) | | | Quartile 2 (N = 40) | | | Quartile 3 (N = 41) | | | Quartile 4 (N = 40) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| HCT | 45 | 45 | 2.7 | 39-51 | 45 | 45 | 2.2 | 40-50 | 45 | 45 | 2.9 | 38-52 | 45 | 45 | 2.4 | 39-50 |
| HGB | 15.2 | 15.3 | 0.9 | 13.3 – 17.2 | 15.1 | 15.2 | 0.8 | 13.4 – 17.3 | 15.2 | 15.1 | 1.0 | 12.1 – 17.5 | 15.2 | 15.1 | 0.8 | 12.9 – 16.6 |
| RBC | 4.9 | 5.0 | 0.3 | 4.0 – 5.5 | 5.0 | 5.0 | 0.3 | 4.1 – 5.6 | 5.2 | 5.0 | 1.8 | 4.1 – 16.0 | 5.0 | 5.0 | 0.4 | 3.8 – 5.9 |
| WBC | 6.1 | 6.0 | 1.3 | 4.3 – 10.2 | 6.2 | 5.9 | 1.6 | 3.3 – 10.2 | 6.4 | 5.9 | 1.8 | 4.1 – 11.6 | 6.5 | 6.3 | 1.8 | 3.8 – 13.5 |
| Platelets | 206 | 200 | 45 | 126 – 332 | 224 | 222 | 42 | 146 – 353 | 223 | 220 | 47 | 122 – 328 | 216 | 213 | 46 | 132 - 307 |

*No significantly different (P < .05, Bonferroni (Dunn) t test) mean values
**See Table 13 for serum PFOS quartile distribution

# Table 16

## Decatur Male Production Employee (N = 161)
### Urinalysis Results by Quartile of Serum PFOS Distribution*

|  | Quartile 1 N (%) | Quartile 2 N (%) | Quartile 3 N (%) | Quartile 4 N (%) |
|---|---|---|---|---|
| Albumin | 1 (3) | 2 (6) | 1 (3) | 1 (3) |
| Blood | 3 (8) | 4 (10) | 4 (10) | 1 (3) |
| Sugar | 3 (8) | 1 (3) | 2 (1.2) | 0 (0) |

Number of Employees: Q1 = 40; Q2 = 40; Q3 = 41; Q4 = 40
*See Table 13 for serum PFOS quartile distribution

## Table 17

### Decatur Male Non-Production Employee (N = 54)
### Clinical Chemistry Results by Quartile of Serum PFOS Distribution

| | Quartile 1 (N = 13) | | | | Quartile 2 (N = 14) | | | | Quartile 3 (N = 14) | | | | Quartile 4 (N = 13) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| PFOS | 0.19[3,4] | 0.20 | 0.08 | 0.06 – 0.29 | 0.39[4] | 0.39 | 0.06 | 0.32 – 0.49 | 0.71[1,2,4] | 0.70 | 0.16 | 0.50 – 0.98 | 1.66[1,2,3] | 1.19 | 0.73 | 1.00 – 2.95 |
| PFOA | 0.34[4] | 0.21 | 0.54 | 0.04 – 2.10 | 0.34[4] | 0.30 | 0.15 | 0.16 – 0.61 | 0.54[4] | 0.48 | 0.28 | 0.19 – 1.25 | 1.17[1,2,3] | 1.07 | 0.60 | 0.35 – 2.05 |
| TOF | 0.42[2,4] | 0.37 | 0.46 | 0.08 – 1.90 | 0.64[4] | 0.60 | 0.21 | 0.40 – 1.12 | 0.98[1,4] | 0.96 | 0.24 | 0.64 – 1.39 | 2.29[1,2,3] | 1.88 | 0.91 | 1.13 – 3.74 |
| Age | 42 | 44 | 10 | 27 – 59 | 42 | 36 | 13 | 28 – 60 | 48 | 51 | 8 | 30 – 56 | 49 | 51 | 6 | 35 – 56 |
| BMI | 29.5 | 27.4 | 6.0 | 22.7 – 40.8 | 26.3 | 25.5 | 4.0 | 21.7 – 35.4 | 29.1 | 28.7 | 3.4 | 25.5 – 37.3 | 28.7 | 29.4 | 2.3 | 24 – 32 |
| Years Worked | 15.1 | 18.7 | 11.9 | 0.8 – 37.9 | 19.6 | 17.3 | 13.8 | 2.2 – 38.5 | 24.3 | 28.6 | 11.6 | 2.3 – 34.2 | 27.8[1] | 31.8 | 8.6 | 4.5 – 35.4 |
| Cigarettes/day | 5 | 0 | 13 | 0 – 40 | 5 | 0 | 11 | 0 – 40 | 2 | 0 | 8 | 0 – 30 | 8 | 0 | 15 | 0 – 40 |
| Drinks/day | 0.2 | 0 | 0.3 | 0 – 0.8 | 0.3 | 0 | 0.7 | 0 – 2.0 | 0.2 | 0 | 0.5 | 0 – 1.6 | 0.1 | 0 | 0.2 | 0 – 0.8 |
| Cholesterol | 207 | 199 | 45 | 158 – 305 | 204 | 192 | 42 | 153 – 278 | 203 | 197 | 48 | 144 – 281 | 222 | 233 | 42 | 159 – 297 |
| HDL | 46 | 40 | 14 | 32 – 82 | 49 | 46 | 14 | 35 – 80 | 43 | 40 | 8 | 34 – 59 | 43 | 42 | 12 | 24 – 73 |
| Triglycerides | 157 | 185 | 63 | 38 – 254 | 129 | 96 | 64 | 59 – 241 | 161 | 154 | 65 | 62 – 284 | 232 | 122 | 173 | 69 – 512 |
| Alk Phos | 59 | 61 | 15 | 26 – 79 | 62 | 62 | 17 | 39 – 98 | 72 | 72 | 15 | 48 – 105 | 75 | 73 | 15 | 52 – 104 |
| GGT | 22 | 21 | 8 | 11 – 35 | 36 | 25 | 29 | 13 – 119 | 29 | 29 | 8 | 15 – 41 | 29 | 23 | 22 | 9 – 89 |
| AST | 25 | 22 | 7 | 16 – 42 | 28 | 27 | 10 | 16 – 48 | 27 | 25 | 6 | 16 – 39 | 22 | 23 | 5 | 14 – 29 |
| ALT | 28 | 23 | 16 | 15 – 74 | 33 | 32 | 20 | 14 – 91 | 35 | 33 | 12 | 24 – 66 | 28 | 27 | 6 | 20 – 41 |
| Total Bilirubin | 0.8 | 0.8 | 0.2 | 0.5 – 1.0 | 0.8 | 0.8 | 0.2 | 0.5 – 1.0 | 0.8 | 0.7 | 0.3 | 0.4 – 1.4 | 0.8 | 0.8 | 0.2 | 0.4 – 1.1 |
| Direct Bilirubin | 0.1 | 0.1 | 0.07 | 0.0 – 0.2 | 0.1 | 0.1 | 0.03 | 0.1 – 0.2 | 0.1 | 0.1 | 0.06 | 0.0 – 0.2 | 0.1 | 0.1 | 0.07 | 0.1 – 0.3 |
| BUN | 14 | 13 | 3 | 8 – 22 | 14 | 14 | 3 | 10 – 18 | 15 | 15 | 5 | 8 – 24 | 16 | 14 | 4 | 12 – 22 |
| Creatinine | 1.0 | 1.0 | 0.1 | 0.9 – 1.2 | 1.0 | 1.1 | 0.1 | 0.8 – 1.1 | 1.1 | 1.1 | 0.2 | 0.7 – 1.4 | 1.1 | 1.1 | 0.1 | 1.0 – 1.3 |
| Glucose | 88 | 89 | 8 | 76 – 99 | 89 | 89 | 6 | 79 – 100 | 94 | 92 | 10 | 70 – 112 | 103 | 91 | 26 | 83 – 166 |

different (P ≤ .05, Bonferroni (Dunn) t test) from the mean of the 1st quartile
...the mean of the 2nd quartile

Table 18

Decatur Male Non-Production Employee (N = 54)
Thyroid Results by Quartile of Serum PFOS Distribution**

| | Quartile 1 (N = 13) | | | | Quartile 2 (N = 14) | | | | Quartile 3 (N = 14) | | | | Quartile 4 (N = 13) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| TSH | 2.1 | 1.8 | 1.0 | 0.8 – 4.2 | 2.1 | 1.9 | 1.3 | 0.03 – 5.2 | 3.0 | 2.0 | 2.7 | 1.6 – 11.8 | 1.6 | 1.5 | 0.9 | 0.4 – 3.6 |
| T4 | 9.1 | 9.1 | 1.2 | 6.9 – 10.9 | 8.2 | 7.9 | 1.6 | 6.2 – 10.7 | 8.0 | 8.2 | 1.3 | 6.3 – 10.2 | 8.7 | 8.7 | 1.2 | 7.0 – 10.9 |
| Free T4 | 1.1 | 1.1 | 0.1 | 0.1 – 1.3 | 1.1 | 1.1 | 0.1 | 0.9 – 1.3 | 1.0 | 1.1 | 0.1 | 0.8 – 1.2 | 1.2 | 1.2 | 0.1 | 0.9 – 1.4 |
| T3 | 124 | 129 | 17 | 99 – 150 | 120 | 112 | 23 | 94 – 180 | 117 | 114 | 23 | 86 – 164 | 118 | 121 | 13 | 91 – 136 |
| THBR | 30 | 30 | 2 | 29 – 34 | 31 | 31 | 3 | 25 – 35 | 31 | 31 | 3 | 26 – 35 | 30 | 31 | 3 | 25 – 36 |
| FTI | 2.7 | 2.8 | 0.4 | 2.0 – 3.4 | 2.4 | 2.6 | 0.4 | 1.8 – 3.2 | 2.4 | 2.5 | 0.5 | 1.7 – 3.1 | 2.6 | 2.5 | 0.4 | 2.0 – 3.2 |

*No significantly different (P < .05, Bonferroni (Dunn) t test) mean values
**See Table 17 for serum PFOS quartile distribution

Table 19

Decatur Male Non-Production Employee (N = 54)
Hematology Results* by Quartile of Serum PFOS Distribution**

| | Quartile 1 (N = 13) | | | Quartile 2 (N = 14) | | | Quartile 3 (N = 14) | | | Quartile 4 (N = 13) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| HCT | 45 | 45 | 3 | 38 – 51 | 45 | 45 | 3 | 41 – 53 | 44 | 45 | 3 | 41 – 49 | 45 | 45 | 1 | 43 – 49 |
| HGB | 15.2 | 15.4 | 1.2 | 12.0 – 16.9 | 15.4 | 15.0 | 1.1 | 14.2 – 17.8 | 14.9 | 15.0 | 0.8 | 13.6 – 16.7 | 15.0 | 15.1 | 0.5 | 14.0 – 16.0 |
| RBC | 5.0 | 5.0 | 0.3 | 4.7 – 5.5 | 5.6 | 4.9 | 2.8 | 4.5 – 15.1 | 4.8 | 4.8 | 0.3 | 4.3 – 5.3 | 5.1 | 5.1 | 0.3 | 4.6 – 5.5 |
| WBC | 6.1 | 5.7 | 2.2 | 4.1 – 13.1 | 6.0 | 6.1 | 1.6 | 3.0 – 8.2 | 6.0 | 5.7 | 1.1 | 4.4 – 8.6 | 6.4 | 6.0 | 1.6 | 4.4 – 9.8 |
| Platelets | 245 | 223 | 62 | 134 – 337 | 219 | 217 | 30 | 172 – 266 | 230 | 206 | 58 | 149 – 361 | 212 | 203 | 34 | 167 - 258 |

*No significantly different (P < .05, Bonferroni (Dunn) t test) mean values
**See Table 17 for serum PFOS quartile distribution

Table 20

Decatur Male Non-Production Employee (N = 54)
Urinalysis Results by Quartile of Serum PFOS Distribution*

|  | Quartile 1 N (%) | Quartile 2 N (%) | Quartile 3 N (%) | Quartile 4 N (%) |
|---|---|---|---|---|
| Albumin | 0 (0) | 0 (0) | 0 (0) | 1 (8) |
| Blood | 2 (15) | 0 (0) | 2 (15) | 0 (0) |
| Sugar | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

Number of Employees: Q1 = 13; Q2 = 14; Q3 = 14; Q4 = 13
*See Table 17 for serum PFOS quartile distribution

## Table 21

### Decatur Female Production and Non-Production Employee (N = 48)
### Clinical Chemistry Results by Quartile of Serum PFOS Distribution

| | Quartile 1 (N = 12) | | | | Quartile 2 (N = 12) | | | | Quartile 3 (N = 12) | | | | Quartile 4 (N = 12) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| PFOS | 0.20[3,4] | 0.20 | 0.08 | 0.06 – 0.31 | 0.49[3,4] | 0.50 | 0.13 | 0.32 – 0.70 | 0.99[1,2,4] | 0.92 | 0.16 | 0.77 – 1.30 | 2.04[1,2,3] | 1.80 | 0.78 | 1.38 – 3.62 |
| PFOA | 0.40[3,4] | 0.28 | 0.47 | 0.08 – 1.81 | 0.78[3,4] | 0.60 | 0.92 | 0.10 – 3.50 | 1.77[1,2] | 1.28 | 1.17 | 0.25 – 4.00 | 1.98[1,2] | 1.54 | 1.27 | 0.85 – 5.41 |
| TOF | 0.48[3,4] | 0.34 | 0.38 | 0.21 – 1.60 | 1.02[4] | 0.94 | 0.72 | 0.33 – 3.02 | 2.14[1,4] | 1.83 | 0.88 | 0.86 – 3.54 | 3.39[1,2,3] | 2.76 | 1.65 | 1.99 – 7.81 |
| Age | 36 | 36 | 8 | 25 – 47 | 43 | 43 | 11 | 26 – 58 | 44 | 43 | 6 | 32 – 50 | 44 | 46 | 7 | 30 – 52 |
| BMI | 27.5 | 27.4 | 6.8 | 21.5 – 45.3 | 25.9 | 25.5 | 5.4 | 20.0 – 39.3 | 27.5 | 28.2 | 4.5 | 20.3 – 33.6 | 29.9 | 27.8 | 6.8 | 21.0 – 41.5 |
| Years Worked | 11 | 7 | 10 | 2 – 27 | 14 | 13 | 11 | 2 – 27 | 12 | 6 | 10 | 4 – 32 | 15 | 17 | 10 | 3 – 32 |
| Cigarettes/day | 2 | 0 | 5 | 0 – 15 | 3 | 0 | 9 | 0 – 30 | 4 | 0 | 9 | 0 – 30 | 13 | 5 | 15 | 0 – 40 |
| Drinks/day | 0.0 | 0 | 0.1 | 0.0 – 0.3 | 0.1 | 0.0 | 0.2 | 0.0 – 1.0 | 0.0 | 0 | 0.1 | 0.0 – 0.1 | 0.1 | 0.0 | 0.1 | 0.0 – 0.3 |
| Cholesterol | 184 | 170 | 40 | 138 – 266 | 202 | 210 | 31 | 139 – 262 | 206 | 200 | 43 | 161 – 313 | 209 | 206 | 42 | 129 – 287 |
| HDL | 55 | 56 | 11 | 33 – 69 | 60 | 58 | 12 | 40 – 81 | 66 | 66 | 12 | 50 – 91 | 55 | 55 | 12 | 36 – 78 |
| Triglycerides | 96 | 100 | 49 | 24 – 198 | 109 | 89 | 58 | 41 – 233 | 186 | 94 | 281 | 42 – 1049 | 142 | 113 | 94 | 46 – 394 |
| Alk Phos | 59 | 61 | 16 | 27 – 81 | 63 | 58 | 19 | 34 – 91 | 68 | 69 | 22 | 41 – 100 | 70 | 70 | 15 | 44 – 95 |
| GGT | 14 | 15 | 6 | 6 – 26 | 14 | 13 | 6 | 7 – 30 | 28 | 17 | 27 | 10 – 97 | 16 | 13 | 9 | 6 – 39 |
| AST | 22 | 21 | 8 | 13 – 43 | 18 | 18 | 5 | 11 – 26 | 21 | 19 | 9 | 7 – 39 | 18 | 17 | 5 | 11 – 30 |
| ALT | 20 | 16 | 13 | 9 – 58 | 18 | 17 | 7 | 11 – 36 | 22 | 17 | 12 | 6 – 47 | 17 | 14 | 6 | 10 – 29 |
| Total Bilirubin | 0.6 | 0.6 | 0.2 | 0.2 – 0.9 | 0.6 | 0.6 | 0.2 | 0.3 – 1.0 | 0.6 | 0.5 | 0.1 | 0.4 – 0.8 | 0.5 | 0.5 | 0.1 | 0.3 – 0.7 |
| Direct Bilirubin | 0.1 | 0.1 | 0.1 | 0.0 – 0.2 | 0.1 | 0.1 | 0.05 | 0.0 – 0.1 | 0.1 | 0.1 | 0.04 | 0.0 – 0.1 | 0.1 | 0.1 | 0.05 | 0.0 – 0.1 |
| BUN | 12 | 13 | 4 | 5 – 20 | 12 | 13 | 3 | 8 – 17 | 13 | 13 | 4 | 6 – 23 | 12 | 13 | 5 | 1 – 18 |
| Creatinine | 0.8 | 0.8 | 0.2 | 0.6 – 1.1 | 0.8 | 0.8 | 0.1 | 0.7 – 1.2 | 0.9 | 0.9 | 0.2 | 0.6 – 1.2 | 0.9 | 0.8 | 0.1 | 0.7 – 1.1 |
| Glucose | 89 | 90 | 15 | 73 – 125 | 86 | 86 | 9 | 72 – 110 | 82 | 85 | 8 | 67 – 90 | 92 | 89 | 13 | 78 – 123 |

*Number of Female employees by production category by quartile

[1] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 1st quartile
[2] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 2nd quartile
[3] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 3rd quartile
[4] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 4th quartile

Table 22

Decatur Female Production and Non-Production Employee (N = 48)
Thyroid Results* by Quartile of Serum PFOS Distribution**

| | Quartile 1 (N = 12) | | | | Quartile 2 (N = 12) | | | | Quartile 3 (N = 12) | | | | Quartile 4 (N = 12) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| TSH | 2.0 | 2.0 | 1.3 | 0.03 – 4.8 | 2.6 | 2.2 | 1.3 | 0.7 – 4.6 | 2.4 | 2.1 | 1.2 | 1.0 – 5.2 | 2.2 | 2.2 | 0.6 | 1.4 – 3.6 |
| T4 | 10.0 | 9.8 | 2.7 | 6.5 – 15.1 | 9.0 | 8.9 | 2.0 | 5.8 – 12.2 | 9.2 | 8.9 | 1.7 | 6.7 – 11.9 | 9.1 | 8.4 | 2.5 | 5.8 – 14.2 |
| Free T4 | 1.0 | 1.1 | 0.1 | 0.9 – 1.3 | 1.1 | 1.0 | 0.1 | 0.9 – 1.3 | 1.0 | 1.0 | 0.1 | 0.7 – 1.1 | 1.0 | 1.0 | 0.1 | 0.8 – 1.2 |
| T3 | 132 | 126 | 26 | 102 – 188 | 127 | 120 | 29 | 86 – 176 | 126 | 119 | 26 | 91 – 168 | 127 | 122 | 32 | 86 – 196 |
| THBR | 28 | 29 | 3 | 24 – 34 | 28 | 28 | 3 | 23 – 36 | 26 | 26 | 4 | 22 – 32 | 28 | 28 | 4 | 18 – 32 |
| FTI | 2.7 | 2.7 | 0.6 | 1.7 – 3.8 | 2.5 | 2.5 | 0.5 | 1.7 – 3.1 | 2.3 | 2.4 | 0.4 | 1.6 – 2.7 | 2.4 | 2.4 | 0.4 | 1.8 – 3.0 |

*No significantly different (P < .05, Bonferroni (Dunn) t test) mean values
**See Table 21 for serum PFOS quartile distribution

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Table 23

Decatur Female Production and Non-Production Employee (N = 48)
Hematology Results by Quartile of Serum PFOS Distribution*

| | Quartile 1 (N = 12) | | | | Quartile 2 (N = 12) | | | | Quartile 3 (N = 12) | | | | Quartile 4 (N = 12) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| HCT | 38 | 38 | 3 | 31 – 43 | 40 | 40 | 2 | 36 – 43 | 39 | 39 | 1 | 36 – 41 | 40 | 40 | 4 | 34 – 49 |
| HGB | 12.6 | 12.7 | 1.2 | 9.9 – 14.4 | 13.3 | 13.3 | 0.6 | 12.3 – 14.5 | 12.9 | 12.8 | 0.5 | 12.0 – 13.8 | 13.4 | 13.4 | 1.4 | 11.3 – 16.2 |
| RBC | 4.3 | 4.3 | 0.3 | 3.8 – 4.8 | 4.3 | 4.3 | 0.3 | 3.7 – 4.8 | 4.4 | 4.3 | 0.3 | 3.9 – 5.0 | 4.3 | 4.4 | 0.4 | 3.9 – 5.0 |
| WBC | 6.7 | 6.3 | 2.0 | 4.2 – 11.7 | 6.6 | 6.5 | 1.9 | 4.3 – 10.4 | 5.9 | 6.2 | 1.7 | 2.8 – 8.4 | 7.6 | 7.5 | 1.9 | 4.2 – 10.4 |
| Platelets | 280[3] | 260 | 68 | 212 – 450 | 228 | 216 | 42 | 185 – 302 | 209[1] | 206 | 34 | 147 – 272 | 258 | 254 | 55 | 159 – 339 |

*See Table 21 for serum PFOS quartile distribution
[1] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 1st quartile
[2] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 2nd quartile
[3] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 3rd quartile
[4] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 4th quartile

Table 24

Decatur Female Production and Non-Production Employee (N = 48)
Urinalysis Results by Quartile of Serum PFOS Distribution*

| | Quartile 1 N (%) | Quartile 2 N (%) | Quartile 3 N (%) | Quartile 4 N (%) |
|---|---|---|---|---|
| Albumin | 0 (0) | 0 (0) | 2 (17) | 0 (0) |
| Blood | 2 (17) | 0 (0) | 3 (25) | 0 (0) |
| Sugar | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

Number of Employees: Q1 = 12; Q2 = 12; Q3 = 12; Q4 = 12
*See Table 21 for serum PFOS quartile distribution

Table 25

Number of Participants (Percent in Parenthesis) Stratified by Antwerp or Decatur Employee Populations
Who Had Above Reference Range Values for Hepatic Clinical Chemistry Tests by Quartile of Serum PFOS Distribution

| | Alkaline Phosphatase | | | | AST | | | | ALT | | | | GGT | | | | Total Liver Panel* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| **Antwerp** | | | | | | | | | | | | | | | | | | | | |
| Male Production[1] | 0(0) | 0(0) | 0(0) | 0(0) | 1(3) | 0(0) | 0(0) | 0(0) | 1(3) | 0(0) | 0(0) | 0(0) | 1(3) | 1(3) | 2(5) | 4(11) | 3(8) | 5(13) | 4(11) | 5(14) |
| Male Non-Production[2] | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 1(7) | 0(0) | 1(8) | 0(0) | 0(0) | 1(7) | 1(8) | 2(13) | 1(7) | 2(14) | 2(15) | 3(20) | 1(8) |
| Female Production[3] and Non-Production | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 1(8) | 0(0) | 0(0) |
| **Decatur** | | | | | | | | | | | | | | | | | | | | |
| Male Production[4] | 1(3) | 2(6) | 2(6) | 1(3) | 0(0) | 1(3) | 0(0) | 4(10) | 3(8) | 5(13) | 3(8) | 11(28) | 4(10) | 3(8) | 2(6) | 6(15) | 7(18) | 8(20) | 7(18) | 14(35) |
| Male Non-Production[5] | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 2(14) | 0(0) | 0(0) | 1(8) | 1(7) | 2(14) | 0(0) | 0(0) | 3(21) | 0(0) | 1(8) | 1(8) | 5(36) | 2(14) | 1(8) |
| Female Production[6] and Non-Production | 0(0) | 0(0) | 0(0) | 0(0) | 1(8) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 2(17) | 0(0) | 1(8) | 0(0) | 2(17) | 0(0) |

*Include Alkaline Phosphate, AST, ALT, GGT, Total and Direct Bilirubin
[1] See Table 4 for serum PFOS quartile distribution
[2] See Table 7 for serum PFOS quartile distribution
[3] See Table 10 for serum PFOS quartile distribution
[4] See Table 13 for serum PFOS quartile distribution
[5] See Table 17 for serum PFOS quartile distribution
[6] See Table 21 for serum PFOS quartile distribution

Table 26

Antwerp and Decatur Male Production and Non-Production* (N = 421)
Fluorochemical, Demographic and Clinical Chemistry Results by Quartile of Serum PFOS Distribution

| | Quartile 1 (N = 105) | | | | Quartile 2 (N = 105) | | | | Quartile 3 (N = 106) | | | | Quartile 4 (N = 105) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| PFOS | 0.27[2,3,4] | 0.29 | 0.11 | 0.04 – 0.42 | 0.60[1,3,4] | 0.59 | 0.12 | 0.43 – 0.81 | 1.19[1,2,4] | 1.17 | 0.24 | 0.82 – 1.68 | 2.69[1,2,3] | 2.46 | 1.09 | 1.69 – 10.06 |
| PFOA | 0.54[2,3,4] | 0.25 | 0.77 | 0.01 – 4.03 | 1.21[1,4] | 0.86 | 1.19 | 0.06 – 7.04 | 1.45[1,4] | 1.20 | 1.10 | 0.12 – 7.48 | 2.70[1,2,3] | 2.43 | 1.63 | 0.25 – 12.70 |
| TOF | 0.62[2,3,4] | 0.43 | 0.58 | 0.05 – 3.03 | 1.40[1,3,4] | 1.14 | 0.89 | 0.38 – 5.69 | 2.12[1,2,4] | 1.88 | 0.87 | 0.98 – 6.61 | 4.41[1,2,3] | 4.06 | 1.72 | 1.92 – 12.23 |
| Age | 38[3] | 36 | 10 | 23 – 60 | 41 | 40 | 10 | 21 – 63 | 42[1] | 43 | 9 | 22 – 61 | 40 | 40 | 9 | 27 – 60 |
| BMI | 25.8 | 25.1 | 4.0 | 19.2 – 40.8 | 26.9 | 26.3 | 4.0 | 19.0 – 37.3 | 27.3 | 26.7 | 4.5 | 17.2 – 50.1 | 27.2 | 26.8 | 4.5 | 17.8 – 45.5 |
| Years Worked | 12[3] | 11 | 10 | 1 – 38 | 15 | 11 | 12 | 2 – 38 | 16[1] | 16 | 11 | 1 – 38 | 15 | 15 | 10 | 2 – 38 |
| Cigarettes/day | 4 | 0 | 9 | 0 – 40 | 5 | 0 | 10 | 0 – 40 | 6 | 0 | 10 | 0 – 40 | 6 | 0 | 10 | 0 – 40 |
| Drinks/day | 0.9[3,4] | 0.7 | 1.0 | 0 – 5 | 0.6 | 0.3 | 0.9 | 0 – 4 | 0.5[1] | 0.1 | 0.9 | 0 – 6 | 0.5[1] | 0.0 | 0.9 | 0 – 5 |
| Cholesterol | 214. | 209 | 41 | 140 – 331 | 214 | 217 | 43 | 121 – 308 | 215 | 216 | 39 | 105 – 303 | 222 | 214 | 44 | 122 – 384 |
| HDL | 54 | 53 | 15 | 31 – 121 | 47 | 45 | 11 | 29 – 80 | 48 | 46 | 13 | 24 – 100 | 48 | 45 | 15 | 26 – 119 |
| Triglycerides | 131[4] | 104 | 95 | 32 – 527 | 155 | 130 | 102 | 35 – 633 | 169 | 134 | 123 | 32 – 731 | 177[1] | 155 | 123 | 39 – 796 |
| Alk Phos | 61[3,4] | 62 | 16 | 26 – 98 | 67 | 66 | 18 | 30 – 142 | 69[1] | 67 | 21 | 30 – 160 | 70[1] | 67 | 19 | 21 – 126 |
| GGT | 24 | 20 | 16 | 7 – 111 | 29 | 22 | 22 | 7 – 144 | 26 | 23 | 15 | 6 – 89 | 30 | 25 | 17 | 7 – 85 |
| AST | 25 | 24 | 8 | 13 – 58 | 25 | 24 | 6 | 16 – 49 | 24 | 24 | 7 | 7 – 51 | 25 | 24 | 9 | 13 – 69 |
| ALT | 26[4] | 23 | 13 | 10 – 91 | 28 | 26 | 11 | 10 – 63 | 28 | 26 | 14 | 6 – 103 | 33[1] | 29 | 19 | 8 – 99 |
| Total Bilirubin | 1.0[3,4] | 0.9 | 0.3 | 0.5 – 2.0 | 0.9 | 0.8 | 0.3 | 0.3 – 2.0 | 0.8[1] | 0.8 | 0.3 | 0.4 – 2.0 | 0.8[1] | 0.7 | 0.3 | 0.4 – 2.2 |
| Direct Bilirubin | 0.1 | 0.1 | 0.1 | 0.0 – 0.3 | 0.1 | 0.1 | 0.1 | 0.0 – 0.7 | 0.1 | 0.1 | 0.1 | 0.0 – 0.3 | 0.1 | 0.1 | 0.1 | 0.0 – 0.6 |
| BUN | 18 | 17 | 7 | 8 – 71 | 17 | 17 | 4 | 9 – 30 | 17 | 16 | 5 | 8 – 31 | 17 | 16 | 5 | 6 – 30 |
| Creatinine | 1.2 | 1.1 | 0.5 | 0.8 – 5.8 | 1.1 | 1.1 | 0.2 | 0.7 – 1.7 | 1.3 | 1.1 | 1.4 | 0.8 – 15.0 | 1.1 | 1.0 | 0.2 | 0.8 – 1.5 |
| Glucose | 87 | 89 | 16 | 31 – 131 | 91 | 90 | 17 | 49 – 184 | 91 | 91 | 17 | 45 – 168 | 91 | 89 | 30 | 40 – 331 |

Table 26 (continued)

*Number of male employees by location, production category and quartile (percent in parenthesis)

| | Quartile 1 | | Quartile 2 | | Quartile 3 | | Quartile 4 | |
|---|---|---|---|---|---|---|---|---|
| | Production | Non-Production | Production | Non-Production | Production | Non-Production | Production | Non-Production |
| Antwerp | 38 | 38 | 38 | 12 | 38 | 4 | 36 | 2 |
| Decatur | 7 | 22 | 40 | 15 | 51 | 13 | 63 | 4 |
| Total | 45 (43) | 60 (57) | 78 (74) | 27 (26) | 89 (84) | 27 (16) | 99 (94) | 6 (6) |

[1] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 1st quartile
[2] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 2nd quartile
[3] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 3rd quartile
[4] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 4th quartile

Table 27

Antwerp and Decatur Male Production and Non-Production Employee (N = 421)
Thyroid Results by Quartile of Serum PFOS Distribution*

| | Quartile 1 (N = 105) | | | | Quartile 2 (N = 105) | | | | Quartile 3 (N = 106) | | | | Quartile 4 (N = 105) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| TSH | 2.0 | 1.9 | 1.2 | 0.03 – 5.7 | 3.1 | 2.0 | 6.6 | 0.5 – 65.3 | 2.1 | 1.7 | 2.0 | 0.2 – 18.8 | 2.5 | 1.9 | 2.8 | 0.5 – 21.5 |
| T4 | 8.3 | 8.5 | 1.4 | 5.0 – 11.5 | 8.2 | 8.4 | 1.4 | 4.2 – 12.0 | 8.3 | 8.2 | 1.5 | 3.3 – 12.9 | 8.4 | 8.2 | 1.4 | 4.7 – 11.4 |
| Free T4 | 1.1 | 1.1 | 0.2 | 0.9 – 1.5 | 1.1 | 1.1 | 0.1 | 0.6 – 1.4 | 1.1 | 1.1 | 0.2 | 0.4 – 1.6 | 1.1 | 1.2 | 0.2 | 0.8 – 1.6 |
| T3 | 124[4] | 123 | 17 | 94 – 164 | 128 | 127 | 20 | 86 – 186 | 127 | 126 | 21 | 91 – 196 | 132[1] | 131 | 22 | 87 – 190 |
| THBR | 33[3,4] | 33 | 3 | 26 – 42 | 32 | 33 | 3 | 24 – 41 | 32[1] | 32 | 3 | 25 – 43 | 32[1] | 32 | 3 | 25 – 41 |
| FTI | 2.7 | 2.7 | 0.5 | 1.7 – 4.2 | 2.6 | 2.5 | 0.4 | 1.2 – 4.0 | 2.6 | 2.6 | 0.5 | 1.0 – 4.1 | 2.6 | 2.6 | 0.4 | 1.6 – 3.6 |

*See Table 26 for serum PFOS distribution
[1] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 1st quartile
[2] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 2nd quartile
[3] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 3rd quartile
[4] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 4th quartile

Table 28

Antwerp and Decatur Female Production and Non-Production (N = 97)
Fluorochemical, Demographic and Clinical Chemistry Results by Quartile of Serum PFOS Distribution

| | Quartile 1 (N = 24) | | | | Quartile 2 (N = 24) | | | | Quartile 3 (N = 25) | | | | Quartile 4 (N = 24) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| PFOS | 0.07[3,4] | 0.08 | 0.02 | 0.04 – 0.10 | 0.13[4] | 0.13 | 0.03 | 0.10 – 0.19 | 0.39[1] | 0.37 | 0.15 | 0.20 – 0.70 | 1.51[1,2,3] | 1.34 | 0.76 | 0.77 – 3.62 |
| PFOA | 0.04[3,4] | 0.02 | 0.04 | 0.01 – 0.23 | 0.07[4] | 0.05 | 0.07 | 0.02 – 0.34 | 0.61[1] | 0.36 | 0.74 | 0.04 – 3.50 | 1.88[1,2,3] | 1.39 | 1.20 | 0.25 – 5.41 |
| TOF | 0.09[3,4] | 0.09 | 0.04 | 0.05 – 0.26 | 0.17[3,4] | 0.14 | 0.07 | 0.09 – 0.35 | 0.80[1,2,4] | 0.59 | 0.61 | 0.21 – 3.02 | 2.77[1,2,3] | 2.66 | 1.44 | 0.86 – 7.81 |
| Age | 34[4] | 34 | 9 | 24 – 52 | 37[4] | 36 | 7 | 25 – 52 | 39 | 38 | 9 | 25 – 58 | 44[1,2] | 45 | 6 | 30 – 52 |
| BMI | 22.8[4] | 23.4 | 2.7 | 18.4 – 28.3 | 23.9[4] | 22.2 | 4.3 | 17.3 – 32.3 | 25.5 | 23.6 | 6.1 | 18.3 – 45.3 | 28.7[1,2] | 27.8 | 5.7 | 20.3 – 41.5 |
| Years Worked | 11 | 9 | 8 | 1 – 29 | 15 | 14 | 7 | 3 – 29 | 12 | 10 | 9 | 2 – 27 | 14 | 12 | 10 | 3 – 32 |
| Cigarettes/day | 1[4] | 0 | 4 | 0 – 20 | 2[4] | 0 | 5 | 0 – 15 | 2 | 0 | 7 | 0 – 30 | 8[1,2] | 0 | 13 | 0 – 40 |
| Drinks/day | 0.4[4] | 0.3 | 0.4 | 0 – 1 | 0.4[4] | 0.3 | 0.4 | 0 – 1 | 0.3 | 0 | 0.4 | 0 – 2 | 0[1,2] | 0 | 0.1 | 0 – 1 |
| Cholesterol | 207. | 203 | 39 | 132 – 274 | 203 | 198 | 39 | 138 – 302 | 200 | 200 | 32 | 139 – 271 | 208 | 202 | 42 | 129 – 313 |
| HDL | 66 | 61 | 16 | 46 – 121 | 65 | 64 | 16 | 33 – 104 | 63 | 61 | 15 | 38 – 104 | 60 | 58 | 13 | 36 – 91 |
| Triglycerides | 93 | 90 | 48 | 26 – 248 | 91 | 88 | 41 | 24 – 172 | 107 | 91 | 53 | 32 – 233 | 164 | 104 | 206 | 42 – 1049 |
| Alk Phos | 50[4] | 52 | 16 | 22 – 81 | 44[3,4] | 44 | 11 | 20 – 65 | 59[2] | 56 | 16 | 32 – 91 | 69[1,2] | 70 | 18 | 41 – 100 |
| GGT | 11[4] | 10 | 7 | 2 – 32 | 13 | 10 | 8 | 5 – 41 | 14 | 12 | 6 | 7 – 30 | 22[1] | 14 | 21 | 6 – 97 |
| AST | 19 | 19 | 5 | 11 – 31 | 18 | 16 | 7 | 9 – 43 | 19 | 19 | 5 | 11 – 33 | 19 | 18 | 7 | 7 – 39 |
| ALT | 13 | 12 | 5 | 8 – 35 | 16 | 13 | 11 | 6 – 58 | 16 | 15 | 6 | 7 – 36 | 19 | 16 | 10 | 6 – 47 |
| Total Bilirubin | 0.8[3,4] | 0.8 | 0.2 | 0.5 – 1.2 | 0.8[3,4] | 0.8 | 0.3 | 0.2 – 1.7 | 0.6[1,2] | 0.6 | 0.2 | 0.3 – 1.0 | 0.5[1,2] | 0.5 | 0.1 | 0.3 – 0.8 |
| Direct Bilirubin | 0.1 | 0.1 | 0.1 | 0.0 – 0.4 | 0.1 | 0.1 | 0.1 | 0.0 – 0.2 | 0.1 | 0.1 | 0.1 | 0.0 – 0.2 | 0.1 | 0.1 | 0.04 | 0.0 – 0.1 |
| BUN | 14 | 13 | 3 | 9 – 23 | 16 | 16 | 4 | 7 – 22 | 14 | 14 | 4 | 5 – 23 | 13 | 13 | 5 | 1 – 23 |
| Creatinine | 0.9 | 0.9 | 0.2 | 0.6 – 1.3 | 1.0 | 1.0 | 0.2 | 0.7 – 1.4 | 0.9 | 0.8 | 0.1 | 0.7 – 1.2 | 0.9 | 0.8 | 0.2 | 0.6 – 1.2 |
| Glucose | 80[2] | 82 | 14 | 38 – 98 | 93[1] | 92 | 13 | 65 – 125 | 85 | 87 | 12 | 49 – 110 | 87 | 87 | 12 | 67 – 123 |

Table 28 (continued)

*Number of female employees by location, production category and quartile (percent in parenthesis)

| | Quartile 1 | | Quartile 2 | | Quartile 3 | | Quartile 4 | |
|---|---|---|---|---|---|---|---|---|
| | Production | Non-Production | Production | Non-Production | Production | Non-Production | Production | Non-Production |
| Antwerp | 3 | 20 | 2 | 17 | 1 | 6 | 0 | 0 |
| Decatur | 0 | 1 | 1 | 4 | 7 | 11 | 22 | 2 |
| Total | 3 (12) | 21 (88) | 3 (12) | 21 (88) | 8 (32) | 17 (68) | 22 (92) | 2 (8) |

[1] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 1st quartile
[2] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 2nd quartile
[3] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 3rd quartile
[4] Mean is significantly different (P < .05, Bonferroni (Dunn) t test) from the mean of the 4th quartile

000191

Table 29

Antwerp and Decatur Female Production and Non-Production Employee (N = 97)
Thyroid Results* by Quartile of Serum PFOS Distribution**

| | Quartile 1 | | | | Quartile 2 | | | | Quartile 3 | | | | Quartile 4 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range | Mean | Median | SD | Range |
| TSH | 2.2 | 2.2 | 1.2 | 0.03 – 4.9 | 2.2 | 2.0 | 1.5 | 0.03 – 6.7 | 2.5 | 2.1 | 1.4 | 0.7 – 6.5 | 2.3 | 2.2 | 1.0 | 1.0 – 5.2 |
| T4 | 10.2 | 10.2 | 2.0 | 6.6 – 13.8 | 9.8 | 9.8 | 3.1 | 4.6 – 18.3 | 9.9 | 9.5 | 2.3 | 5.8 – 15.1 | 9.1 | 8.7 | 2.1 | 5.8 – 14.2 |
| Free T4 | 1.1 | 1.1 | 0.1 | 0.8 – 1.3 | 1.2 | 1.1 | 0.7 | 0.7 – 4.6 | 1.1 | 1.1 | 0.1 | 0.9 – 1.3 | 1.0 | 1.0 | 0.1 | 0.7 – 1.2 |
| T3 | 145 | 147 | 28 | 98 – 191 | 147 | 139 | 53 | 81 – 345 | 133 | 129 | 31 | 86 – 228 | 127 | 120 | 28 | 86 – 196 |
| THBR | 29 | 29 | 4 | 19 – 36 | 31 | 32 | 6 | 22 – 46 | 28 | 27 | 3 | 23 – 36 | 27 | 27 | 4 | 18 – 32 |
| FTI | 2.9 | 2.9 | 0.5 | 2.1 – 3.6 | 3.0 | 2.8 | 1.3 | 1.7 – 8.4 | 2.7 | 2.7 | 0.5 | 1.7 – 3.8 | 2.4 | 2.4 | 0.4 | 1.6 – 3.0 |

*No significantly different (P < .05, Bonferroni (Dunn) t test) mean values
**See Table 28 for serum PFOS quartile distribution

Table 30

## Number of Participants (Percent in Parenthesis) by Employee Population Which Had Above Reference Range Values for Hepatic Clinical Chemistry Tests by Quartile of Serum PFOS Distribution

| | Alkaline Phosphatase | | | | AST | | | | ALT | | | | GGT | | | | Total Liver Panel* | | | |
| | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Antwerp & Decatur** | | | | | | | | | | | | | | | | | | | | |
| **Male Employees** | | | | | | | | | | | | | | | | | | | | |
| Production and Non-Production[1] | 0(0) | 1(1) | 3(3) | 2(2) | 3(3) | 1(1) | 1(1) | 4(4) | 4(4) | 4(4) | 7(7) | 13(12) | 6(6) | 8(8) | 6(6) | 12(12) | 15(14) | 17(16) | 17(16) | 24(23) |
| **Female Employees** | | | | | | | | | | | | | | | | | | | | |
| Production and Non-Production[2] | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 1(4) | 0(0) | 0(0) | 0(0) | 1(4) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 2(8) | 0(0) | 2(8) | 0(0) | 2(8) |

*Include Alkaline Phosphatase, AST, ALT, GGT, Total and Direct Bilirubin

[1] See Table 26 for serum PFOS quartile distribution
[2] See Table 28 for serum PFOS quartile distribution

Table 31

Multivariable Regression Model of Cholesterol* by PFOS
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 5.072 | 0.081 | .0001 | - |
| PFOS | 0.020 | 0.009 | .04 | <.01 |
| Production Job (yes/no) | -0.010 | 0.023 | .66 | <.01 |
| Antwerp/Decatur | -0.025 | 0.025 | .31 | <.01 |
| Age | 0.006 | 0.002 | .0002 | .04 |
| BMI | 0.001 | 0.002 | .62 | <.01 |
| Cigarettes/day | 0.0007 | 0.001 | .49 | <.01 |
| Drinks/day | 0.035 | 0.012 | .004 | .02 |
| Years Worked | -0.002 | 0.001 | .15 | <.01 |

$R^2 = .08$
Adj $R^2 = .06$
*Natural log

Table 32

Multivariable Regression Model of Cholesterol* by PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 5.069 | 0.080 | .0001 | - |
| PFOA | 0.015 | 0.008 | .05 | <.01 |
| Production Job (yes/no) | -0.012 | 0.024 | .63 | <.01 |
| Antwerp/Decatur | -0.032 | 0.025 | .22 | <.01 |
| Age | 0.007 | 0.002 | .0001 | .05 |
| BMI | 0.001 | 0.002 | .64 | <.01 |
| Cigarettes/day | 0.0006 | 0.001 | .52 | <.01 |
| Drinks/day | 0.03 | 0.01 | .005 | .02 |
| Years Worked | -0.002 | 0.001 | .21 | <.01 |

$R^2 = .08$
Adj $R^2 = .06$
*Natural log

Table 33

Multivariable Regression Model of Cholesterol* by PFOS and PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 5.066 | 0.081 | < .0001 | - |
| PFOS | 0.015 | 0.010 | .16 | < .01 |
| PFOA | 0.009 | 0.008 | .26 | < .01 |
| Production Job (yes/no) | - 0.018 | 0.024 | .46 | < .01 |
| Antwerp/Decatur | - 0.033 | 0.025 | .20 | < .01 |
| Age | 0.007 | 0.002 | .0001 | .05 |
| BMI | 0.001 | 0.002 | .62 | < .01 |
| Cigarettes/day | 0.0007 | 0.001 | .50 | < .01 |
| Drinks/day | 0.035 | 0.012 | .004 | .02 |
| Years Worked | - 0.002 | 0.001 | .15 | .004 |

$R^2$ = .08
Adj $R^2$ = .06
*Natural log

Table 34

Multivariable Regression Model of Cholesterol* by TOF
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 5.065 | 0.081 | < .0001 | - |
| TOF | 0.015 | 0.006 | .02 | < .01 |
| Production Job (yes/no) | - 0.018 | 0.024 | .45 | < .01 |
| Antwerp/Decatur | - 0.034 | 0.025 | .18 | < .01 |
| Age | 0.007 | 0.002 | .0001 | .05 |
| BMI | 0.001 | 0.002 | .63 | < .01 |
| Cigarettes/day | 0.0006 | 0.001 | .51 | < .01 |
| Drinks/day | 0.034 | 0.012 | .005 | .02 |
| Years Worked | - 0.002 | 0.001 | .16 | < .01 |

$R^2$ = .08
Adj $R^2$ = .07
*Natural log

Table 35

Multivariable Regression Model of HDL* by PFOS
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 4.313 | 0.090 | <.0001 | - |
| PFOS | -0.005 | 0.011 | .64 | .01 |
| Production Job (yes/no) | 0.009 | 0.026 | .73 | <.01 |
| Antwerp/Decatur | -0.059 | 0.027 | .03 | .17 |
| Age | 0.002 | 0.002 | .37 | <.01 |
| BMI | -0.019 | 0.003 | <.0001 | .07 |
| Cigarettes/day | -0.004 | 0.001 | .0004 | .01 |
| Drinks/day | 0.083 | 0.014 | <.0001 | .06 |
| Years Worked | -0.001 | 0.002 | .51 | <.01 |

$R^2 = .33$
Adj $R^2 = .32$
*Natural log

000198

Table 36

Multivariable Regression Model of HDL* by PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 4.326 | 0.090 | <.0001 | - |
| PFOA | -0.018 | 0.009 | .04 | .04 |
| Production Job (yes/no) | 0.028 | 0.027 | .30 | <.01 |
| Antwerp/Decatur | -0.043 | 0.028 | .13 | .14 |
| Age | 0.001 | 0.002 | .50 | <.01 |
| BMI | -0.019 | 0.003 | <.0001 | .07 |
| Cigarettes/day | -0.004 | 0.001 | .0004 | .01 |
| Drinks/day | 0.084 | 0.014 | <.0001 | .06 |
| Years Worked | -0.001 | 0.002 | .54 | <.01 |

$R^2$ = .34
Adj $R^2$ = .32
*Natural log

Table 37

Multivariable Regression Model of HDL* by PFOS and PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

|  | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 4.324 | 0.090 | <.0001 | - |
| PFOS | 0.006 | 0.012 | .60 | .01 |
| PFOA | -0.020 | 0.010 | .04 | .03 |
| Production Job (yes/no) | 0.025 | 0.271 | .36 | <.01 |
| Antwerp/Decatur | -0.043 | 0.028 | .13 | .14 |
| Age | 0.001 | 0.002 | .50 | <.01 |
| BMI | -0.019 | 0.003 | <.0001 | .07 |
| Cigarettes/day | -0.004 | 0.001 | .0004 | .01 |
| Drinks/day | 0.084 | 0.014 | <.0001 | .06 |
| Years Worked | -0.001 | 0.002 | .49 | <.01 |

$R^2 = .34$
Adj $R^2 = .32$
*Natural log

Table 38

Multivariable Regression Model of HDL* by TOF
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 4.322 | 0.090 | <.0001 | - |
| TOF | -0.010 | 0.007 | .14 | .03 |
| Production Job (yes/no) | 0.022 | 0.027 | .41 | <.01 |
| Antwerp/Decatur | -0.050 | 0.028 | .08 | .15 |
| Age | 0.001 | 0.002 | .45 | <.01 |
| BMI | -0.019 | 0.003 | <.0001 | .07 |
| Cigarettes/day | -0.004 | 0.001 | .0004 | .01 |
| Drinks/day | 0.084 | 0.014 | <.0001 | .06 |
| Years Worked | -0.0009 | 0.002 | .58 | <.01 |

$R^2 = .31$
Adj $R^2 = .32$
*Natural log

Table 39

Multivariable Regression Model of Triglycerides* by PFOS
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 2.768 | 0.224 | <.0001 | - |
| PFOS | 0.066 | 0.026 | .01 | .03 |
| Production Job (yes/no) | 0.023 | 0.065 | .72 | <.01 |
| Antwerp/Decatur | 0.151 | 0.068 | .03 | .10 |
| Age | 0.013 | 0.005 | .009 | .02 |
| BMI | 0.055 | 0.007 | <.0001 | .10 |
| Cigarettes/day | 0.008 | 0.003 | .002 | .02 |
| Drinks/day | 0.033 | 0.034 | .33 | <.01 |
| Years Worked | - 0.007 | 0.004 | .07 | <.01 |

$R^2$ = .28
Adj $R^2$ = .27
*Natural log

Table 40

Multivariable Regression Model of Triglycerides* by PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 2.742 | 0.224 | <.0001 | - |
| PFOA | 0.066 | 0.021 | .002 | .05 |
| Production Job (yes/no) | -0.004 | 0.066 | .95 | <.01 |
| Antwerp/Decatur | 0.111 | 0.070 | .12 | .08 |
| Age. | 0.014 | 0.005 | .005 | .02 |
| BMI | 0.055 | 0.007 | <.0001 | .10 |
| Cigarettes/day | 0.008 | 0.003 | .003 | .02 |
| Drinks/day | 0.029 | 0.034 | .15 | <.01 |
| Years Worked | -0.007 | 0.004 | .11 | .005 |

$R^2 = .29$
Adj $R^2 = .27$
*Natural log

Table 41

Multivariable Regression Model of Triglycerides* by PFOS and PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 2.734 | 0.224 | <.0001 | - |
| PFOS | 0.037 | 0.029 | .20 | .03 |
| PFOA | 0.053 | 0.023 | .02 | .02 |
| Production Job (yes/no) | -0.021 | 0.067 | .76 | <.01 |
| Antwerp/Decatur | 0.109 | 0.070 | .12 | .08 |
| Age | 0.014 | 0.005 | .004 | .02 |
| BMI | 0.055 | 0.007 | <.0001 | .10 |
| Cigarettes/day | 0.008 | 0.003 | .002 | .02 |
| Drinks/day | 0.030 | 0.034 | .15 | <.01 |
| Years Worked | -0.007 | 0.004 | .07 | <.01 |

$R^2 = .29$
Adj $R^2 = .27$
*Natural log

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Table 42

Multivariable Regression Model of Triglycerides* by TOF
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 2.736 | 0.223 | < .0001 | - |
| TOF | 0.056 | 0.017 | .0009 | .06 |
| Production Job (yes/no) | - 0.017 | 0.067 | .81 | < .01 |
| Antwerp/Decatur | 0.113 | 0.070 | .10 | .08 |
| Age. | 0.014 | 0.005 | .005 | .02 |
| BMI | 0.055 | 0.007 | < .0001 | .10 |
| Cigarettes/day | 0.008 | 0.003 | .002 | .02 |
| Drinks/day | 0.030 | 0.034 | .37 | < .01 |
| Years Worked | - 0.007 | 0.004 | .07 | < .01 |

$R^2 = .29$
Adj $R^2 = .27$
*Natural log

Table 43

Multivariable Regression Model of Alkaline Phosphatase* by PFOS
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 3.718 | 0.362 | <.0001 | - |
| PFOS | 0.013 | 0.013 | .32 | .02 |
| Production Job (yes/no) | 0.036 | 0.032 | .26 | <.01 |
| Antwerp/Decatur | 0.149 | 0.034 | <.0001 | .11 |
| Age | 0.0008 | 0.002 | .73 | <.01 |
| BMI | -0.004 | 0.004 | .26 | <.01 |
| Cigarettes/day | 0.002 | 0.001 | .17 | <.01 |
| Drinks/day | -0.024 | 0.016 | .14 | <.01 |
| Years Worked | -0.002 | 0.002 | .41 | <.01 |
| Triglycerides* | 0.083 | 0.024 | .0006 | .02 |

$R^2 = .18$
Adj $R^2 = .16$
*Natural log

; Table 44

## Multivariable Regression Model of Alkaline Phosphatase* by PFOA and Other Potential Explanatory Variables for Antwerp and Decatur Male Employee Participants, 2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 3.746 | 0.128 | <.0001 | - |
| PFOA | 0.0001 | 0.010 | .99 | .03 |
| Production Job (yes/no) | 0.047 | 0.032 | .15 | <.01 |
| Antwerp/Decatur | 0.154 | 0.035 | <.0001 | .10 |
| Age | 0.0006 | 0.002 | .80 | <.01 |
| BMI | - 0.004 | 0.004 | .24 | <.01 |
| Cigarettes/day | 0.002 | 0.001 | .18 | <.01 |
| Drinks/day | - 0.024 | 0.017 | .14 | <.01 |
| Years Worked | - 0.001 | 0.002 | .52 | <.01 |
| Triglycerides* | 0.086 | 0.024 | .0004 | .03 |

$R^2 = .18$
Adj $R^2 = .16$
*Natural log

Table 45

Multivariable Regression Model of Alkaline Phosphatase* by PFOS and PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial R$^2$ |
|---|---|---|---|---|
| Intercept | 3.747 | 0.128 | <.0001 | - |
| PFOS | 0.015 | 0.014 | .28 | .02 |
| PFOA | -0.005 | 0.012 | .65 | <.01 |
| Production Job (yes/no) | 0.040 | 0.033 | .23 | <.01 |
| Antwerp/Decatur | 0.153 | 0.034 | <.0001 | .10 |
| Age | 0.0007 | 0.002 | .78 | <.01 |
| BMI | -0.004 | 0.004 | .25 | <.01 |
| Cigarettes/day | 0.002 | 0.001 | .17 | <.01 |
| Drinks/day | -0.024 | 0.017 | .15 | <.01 |
| Years Worked | -0.002 | 0.002 | .42 | <.01 |
| Triglycerides* | 0.085 | 0.024 | .0005 | .02 |

R$^2$ = .18
Adj R$^2$ = .16
*Natural log

Table 46

Multivariable Regression Model of Alkaline Phosphatase* by TOF
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

Alk Phos

| | Parameter | SE | p value | Partial R² |
|---|---|---|---|---|
| Intercept | 3.747 | 0.128 | <.0001 | - |
| TOF | 0.006 | 0.008 | .47 | .04 |
| Production Job (yes/no) | 0.037 | 0.033 | .27 | <.01 |
| Antwerp/Decatur | 0.147 | 0.034 | <.0001 | .10 |
| Age | 0.0008 | 0.002 | .72 | <.01 |
| BMI | -0.004 | 0.004 | .25 | <.01 |
| Cigarettes/day | 0.002 | 0.001 | .18 | <.01 |
| Drinks/day | -0.024 | 0.016 | .14 | <.01 |
| Years Worked | -0.002 | 0.002 | .45 | <.01 |
| Triglycerides* | 0.084 | 0.024 | .0006 | .02 |

R² = .18
Adj R² = .16
*Natural log

Table 47

Multivariable Regression Model of GGT* by PFOS
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 1.246 | 0.239 | <.0001 | - |
| PFOS | 0.028 | 0.024 | .24 | .03 |
| Production Job (yes/no) | -0.003 | 0.059 | .96 | <.01 |
| Antwerp/Decatur | 0.255 | 0.063 | <.0001 | .07 |
| Age | 0.0003 | 0.004 | .95 | <.01 |
| BMI | 0.006 | 0.007 | .36 | .02 |
| Cigarettes/day | 0.003 | 0.003 | .28 | .01 |
| Drinks/day | 0.117 | 0.031 | .0002 | .03 |
| Years Worked | 0.002 | 0.004 | .45 | <.01 |
| Triglycerides* | 0.294 | 0.045 | <.0001 | .08 |

$R^2 = .25$
Adj $R^2 = .23$
*Natural log

000210

Table 48

Multivariable Regression Model of GGT* by PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 1.245 | 0.238 | <.0001 | - |
| PFOA | 0.032 | 0.019 | 0.10 | .04 |
| Production Job (yes/no) | - 0.020 | 0.060 | .74 | <.01 |
| Antwerp/Decatur | 0.235 | 0.065 | .0003 | .06 |
| Age | 0.0009 | 0.004 | .84 | .01 |
| BMI | 0.006 | 0.007 | .35 | .02 |
| Cigarettes/day | 0.003 | 0.003 | .28 | .01 |
| Drinks/day | 0.116 | 0.031 | .0002 | .03 |
| Years Worked | 0.003 | 0.004 | .40 | <.01 |
| Triglycerides* | 0.289 | 0.045 | <.0001 | .08 |

$R^2 = .25$
Adj $R^2 = .23$
*Natural log

Table 49

Multivariable Regression Model of GGT* by PFOS and PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

|  | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 1.246 | 0.239 | <.0001 | - |
| PFOS | 0.014 | 0.027 | .60 | .03 |
| PFOA | 0.028 | 0.021 | .20 | .02 |
| Production Job (yes/no) | -0.026 | 0.062 | .67 | <.001 |
| Antwerp/Decatur | 0.23 | 0.065 | .0003 | .06 |
| Age | 0.0009 | 0.004 | .82 | .01 |
| BMI | 0.006 | 0.007 | .34 | .02 |
| Cigarettes/day | 0.003 | 0.003 | .27 | .01 |
| Drinks/day | 0.116 | 0.031 | .0002 | .03 |
| Years Worked | 0.003 | 0.004 | .46 | <.01 |
| Triglycerides* | 0.288 | 0.045 | <.0001 | .08 |

$R^2 = .25$
Adj $R^2 = .23$
*Natural log

Table 50

Multivariable Regression Model of GGT* by TOF
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial R² |
|---|---|---|---|---|
| Intercept | 1.246 | 0.238 | <.0001 | - |
| TOF | 0.029 | 0.016 | .06 | .04 |
| Production Job (yes/no) | -0.028 | 0.061 | .64 | <.01 |
| Antwerp/Decatur | 0.235 | 0.064 | .0003 | .06 |
| Age | 0.001 | 0.004 | .82 | .01 |
| BMI | 0.006 | 0.007 | .33 | .02 |
| Cigarettes/day | 0.003 | 0.003 | .28 | .01 |
| Drinks/day | 0.116 | 0.031 | .0002 | .03 |
| Years Worked | 0.003 | 0.003 | .48 | <.01 |
| Triglycerides* | 0.288 | 0.045 | <.0001 | .07 |

R² = .25
Adj R² = .21
*Natural log

Table 51

Multivariable Regression Model of AST* by PFOS
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial R² |
|---|---|---|---|---|
| Intercept | 2.725 | 0.133 | <.0001 | - |
| PFOS | 0.013 | 0.013 | .33 | <.01 |
| Production Job (yes/no) | -0.022 | 0.033 | .50 | <.01 |
| Antwerp/Decatur | 0.114 | 0.035 | .001 | .03 |
| Age | 0.003 | 0.002 | .28 | <.01 |
| BMI | 0.002 | 0.004 | .53 | <.01 |
| Cigarettes/day | -0.003 | 0.001 | .04 | <.01 |
| Drinks/day | 0.052 | 0.017 | .002 | .02 |
| Years Worked | -0.004 | 0.002 | .05 | .01 |
| Triglycerides* | 0.055 | 0.025 | .03 | .01 |

$R^2 = .09$
Adj $R^2 = .07$
*Natural log

000214

Table 52

Multivariable Regression Model of AST* by PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 2.725 | 0.133 | <.0001 | - |
| PFOA | 0.015 | 0.011 | .17 | .01 |
| Production Job (yes/no) | -0.030 | 0.034 | .37 | <.01 |
| Antwerp/Decatur | 0.105 | 0.036 | .004 | .02 |
| Age | 0.003 | 0.002 | .23 | <.01 |
| BMI | 0.002 | 0.004 | .51 | <.01 |
| Cigarettes/day | -0.003 | 0.001 | .04 | <.01 |
| Drinks/day | 0.051 | 0.017 | .003 | .02 |
| Years Worked | -0.004 | 0.002 | .05 | .01 |
| Triglycerides* | 0.053 | 0.025 | .04 | <.01 |

$R^2 = .09$
Adj $R^2 = .07$
*Natural log

Table 53

Multivariable Regression Model of AST* by PFOS and PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 2.725 | 0.132 | < .0001 | -- |
| PFOS | 0.006 | 0.015 | .68 | < .01 |
| PFOA | 0.013 | 0.012 | .28 | < .01 |
| Production Job (yes/no) | - 0.033 | 0.034 | .34 | < .01 |
| Antwerp/Decatur | 0.104 | 0.036 | .004 | .02 |
| Age | 0.003 | 0.002 | .23 | < .01 |
| BMI | 0.002 | 0.004 | .50 | < .01 |
| Cigarettes/day | - 0.003 | 0.001 | .04 | < .01 |
| Drinks/day | 0.052 | 0.017 | .003 | .02 |
| Years Worked | - 0.004 | 0.002 | .04 | .01 |
| Triglycerides* | 0.052 | 0.025 | .04 | < .01 |

$R^2 = .09$
Adj $R^2 = .07$
*Natural log

Table 54

Multivariable Regression Model of AST* by TOF
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

|  | Parameter | SE | p value | Partial R$^2$ |
|---|---|---|---|---|
| Intercept | 2.725 | 0.133 | <.0001 | - |
| TOF | 0.011 | 0.009 | .17 | .01 |
| Production Job (yes/no) | -0.031 | 0.034 | .36 | <.01 |
| Antwerp/Decatur | 0.106 | 0.036 | .003 | .02 |
| Age | 0.003 | 0.002 | .24 | <.01 |
| BMI | 0.002 | 0.004 | .51 | <.01 |
| Cigarettes/day | -0.003 | 0.001 | .04 | <.01 |
| Drinks/day | 0.052 | 0.017 | .003 | .02 |
| Years Worked | -0.004 | 0.002 | .04 | .01 |
| Triglycerides* | 0.053 | 0.025 | .04 | <.01 |

R$^2$ = .09
Adj R$^2$ = .07
*Natural log

Table 55

Multivariable Regression Model of ALT* by PFOS
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 1.744 | 0.165 | <.0001 | - |
| PFOS | 0.021 | 0.018 | .25 | .01 |
| Production Job (yes/no) | 0.017 | 0.043 | .69 | <.01 |
| Antwerp/Decatur | 0.172 | 0.042 | <.0001 | .06 |
| Age | -0.002 | 0.003 | .50 | <.01 |
| BMI | 0.025 | 0.004 | <.0001 | .13 |
| Cigarettes/day | -0.007 | 0.002 | .0003 | .01 |
| Drinks/day | -0.006 | 0.024 | .79 | <.01 |
| Years Worked | -0.004 | 0.002 | .10 | <.01 |
| Triglycerides* | 0.189 | 0.032 | <.0001 | .05 |

$R^2 = .27$
Adj $R^2 = .25$
*Natural log

Table 56

Multivariable Regression Model of ALT* by PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

|  | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 1.761 | 0.165 | <.0001 | - |
| PFOA | 0.005 | 0.003 | .13 | <.01 |
| Production Job (yes/no) | 0.027 | 0.041 | .51 | <.01 |
| Antwerp/Decatur | 0.186 | 0.041 | <.0001 | .07 |
| Age | -0.002 | 0.003 | .44 | <.01 |
| BMI | 0.024 | 0.004 | <.0001 | .12 |
| Cigarettes/day | -0.007 | 0.002 | .0002 | .01 |
| Drinks/day | -0.005 | 0.024 | .83 | <.01 |
| Years Worked | -0.004 | 0.002 | .15 | <.01 |
| Triglycerides* | 0.190 | 0.032 | <.0001 | .05 |

$R^2$ = .27
Adj $R^2$ = .25
*Natural log

Table 57

Multivariable Regression Model of ALT* by PFOS and PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 1.757 | 0.165 | <.0001 | - |
| PFOS | 0.019 | 0.018 | .29 | .01 |
| PFOA | 0.004 | 0.003 | .15 | <.01 |
| Production Job (yes/no) | 0.013 | 0.043 | .76 | <.01 |
| Antwerp/Decatur | 0.176 | 0.042 | <.0001 | .06 |
| Age | -0.002 | 0.003 | .50 | <.01 |
| BMI | 0.025 | 0.004 | <.0001 | .12 |
| Cigarettes/day | -0.007 | 0.002 | .0003 | <.01 |
| Drinks/day | -0.006 | 0.024 | .80 | <.01 |
| Years Worked | -0.004 | 0.002 | .11 | <.01 |
| Triglycerides* | 0.187 | 0.032 | <.0001 | .05 |

$R^2 = .27$
Adj $R^2 = .26$
*Natural log

Table 58

Multivariable Regression Model of ALT* by TOF
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

|  | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 1.965 | 0.193 | <.0001 | - |
| TOF | 0.029 | 0.013 | .02 | .06 |
| Production Job (yes/no) | -0.054 | 0.050 | .27 | <.01 |
| Antwerp/Decatur | 0.296 | 0.051 | <.0001 | .15 |
| Age | -0.003 | 0.004 | .38 | <.01 |
| BMI | 0.012 | 0.005 | .02 | .04 |
| Cigarettes/day | -0.007 | 0.002 | .0003 | .01 |
| Drinks/day | 0.01 | 0.025 | .62 | <.01 |
| Years Worked | -0.002 | 0.003 | .44 | <.01 |
| Triglycerides* | 0.199 | 0.04 | <.0001 | .05 |

$R^2 = .32$
Adj $R^2 = .31$
*Natural log

Table 59

Multivariable Regression Model of Total Bilirubin* by PFOS
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 0.209 | 0.145 | <.0001 | - |
| PFOS | -0.017 | 0.015 | .25 | .03 |
| Production Job (yes/no) | -0.068 | 0.036 | .06 | .01 |
| Antwerp/Decatur | -0.262 | 0.038 | <.0001 | .18 |
| Age | 0.001 | 0.003 | .58 | <.01 |
| BMI | -0.005 | 0.004 | .19 | <.01 |
| Cigarettes/day | -0.008 | 0.002 | <.0001 | .06 |
| Drinks/day | 0.005 | 0.02 | .80 | <.01 |
| Years Worked | 0.0002 | 0.002 | .94 | <.01 |
| Triglycerides* | -0.015 | 0.027 | .57 | <.01 |

$R^2$ = .29
Adj $R^2$ = .27
*Natural log

Table 60

Multivariable Regression Model of Total Bilirubin* by PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

|  | Parameter | SE | p value | Partial R$^2$ |
|---|---|---|---|---|
| Intercept | 0.210 | 0.145 | <.0001 | - |
| PFOA | - 0.004 | 0.011 | .74 | .05 |
| Production Job (yes/no) | - 0.078 | 0.037 | .04 | .01 |
| Antwerp/Decatur | - 0.265 | 0.039 | <.0001 | .17 |
| Age | 0.002 | 0.003 | .54 | <.01 |
| BMI | - 0.005 | 0.004 | .21 | <.01 |
| Cigarettes/day | - 0.008 | 0.002 | <.0001 | .06 |
| Drinks/day | 0.005 | 0.019 | .80 | <.01 |
| Years Worked | - 0.0002 | 0.002 | .91 | <.01 |
| Triglycerides* | - 0.018 | 0.027 | .52 | <.01 |

R$^2$ = .29
Adj R$^2$ = .2
*Natural log

Table 61

Multivariable Regression Model of Total Bilirubin* by PFOS and PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 0.209 | 0.144 | <.0001 | - |
| PFOS | -0.018 | 0.016 | .27 | .03 |
| PFOA | 0.002 | 0.013 | .86 | .02 |
| Production Job (yes/no) | -0.070 | 0.037 | .063 | .01 |
| Antwerp/Decatur | -0.264 | 0.039 | <.0001 | .16 |
| Age | 0.002 | 0.003 | .57 | <.01 |
| BMI | -0.005 | 0.004 | .20 | <.01 |
| Cigarettes/day | -0.008 | 0.002 | <.0001 | .06 |
| Drinks/day | 0.005 | 0.002 | .81 | <.01 |
| Years Worked | 0.0002 | 0.002 | .95 | <.01 |
| Triglycerides* | -0.016 | 0.027 | .56 | <.01 |

$R^2$ = .29
Adj $R^2$ = .27
*Natural log

Table 62

Multivariable Regression Model of Total Bilirubin* by TOF
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 0.210 | 0.144 | <.0001 | - |
| TOF | -0.011 | 0.009 | .25 | .06 |
| Production Job (yes/no) | -0.064 | 0.037 | .09 | .01 |
| Antwerp/Decatur | -0.257 | 0.039 | <.0001 | .16 |
| Age | 0.001 | 0.003 | .62 | <.01 |
| BMI | -0.005 | 0.004 | .19 | <.01 |
| Cigarettes/day | -0.008 | 0.002 | <.0001 | .06 |
| Drinks/day | 0.005 | 0.019 | .78 | <.01 |
| Years Worked | 0.00007 | 0.002 | .98 | <.01 |
| Triglycerides* | -0.014 | 0.027 | .60 | <.01 |

$R^2 = .29$
Adj $R^2 = .27$
*Natural log

Table 63

Multivariable Regression Model of TSH* by PFOS
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | - 0.539 | 0.327 | .10 | - |
| PFOS | 0.015 | 0.033 | .65 | <.01 |
| Production Job (yes/no) | 0.109 | 0.081 | .18 | <.01 |
| Antwerp/Decatur | 0.184 | 0.086 | .03 | .02 |
| Age | 0.005 | 0.006 | .36 | <.01 |
| BMI | - 0.005 | 0.009 | .56 | <.01 |
| Cigarettes/day | - 0.005 | 0.003 | .17 | <.01 |
| Drinks/day | 0.057 | 0.042 | .17 | <.01 |
| Years Worked | - 0.008 | 0.005 | .13 | <.01 |
| Triglycerides* | 0.204 | 0.061 | .001 | .02 |

$R^2 = .07$
Adj $R^2 = .05$
*Natural log

Table 64

Multivariable Regression Model of TSH* by PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | - 0.539 | 0.327 | .10 | - |
| PFOA | 0.018 | 0.027 | .51 | .02 |
| Production Job (yes/no) | 0.100 | 0.083 | .23 | <.01 |
| Antwerp/Decatur | 0.173 | 0.088 | .051 | <.01 |
| Age | 0.006 | 0.006 | .33 | <.01 |
| BMI | - 0.005 | 0.009 | .56 | <.01 |
| Cigarettes/day | - 0.005 | 0.003 | .17 | <.01 |
| Drinks/day | 0.056 | 0.042 | .18 | <.01 |
| Years Worked | - 0.008 | 0.005 | .13 | <.01 |
| Triglycerides* | 0.201 | 0.062 | .001 | .02 |

$R^2 = .07$
Adj $R^2 = .05$
*Natural log

Table 65

Multivariable Regression Model of TSH* by PFOS and PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | -0.539 | 0.327 | .10 | - |
| PFOS | 0.007 | 0.036 | .85 | <.01 |
| PFOA | 0.015 | 0.029 | .61 | <.01 |
| Production Job (yes/no) | 0.096 | 0.084 | .25 | <.01 |
| Antwerp/Decatur | 0.173 | 0.089 | .05 | <.01 |
| Age | 0.006 | 0.006 | .33 | <.01 |
| BMI | -0.005 | 0.009 | .57 | <.01 |
| Cigarettes/day | -0.005 | 0.003 | .17 | <.01 |
| Drinks/day | 0.056 | 0.042 | .18 | <.01 |
| Years Worked | -0.008 | 0.005 | .13 | <.01 |
| Triglycerides* | 0.200 | 0.062 | .001 | .02 |

$R^2 = .07$
Adj $R^2 = .05$
*Natural log

Table 66

Multivariable Regression Model of TSH* by TOF
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | - 0.539 | 0.327 | .10 | - |
| TOF | 0.015 | 0.021 | .49 | .02 |
| Production Job (yes/no) | 0.097 | 0.084 | .25 | <.01 |
| Antwerp/Decatur | .174 | 0.088 | .05 | .01 |
| Age | 0.006 | 0.006 | .33 | <.01 |
| BMI | - 0.005 | 0.009 | .57 | <.01 |
| Cigarettes/day | - 0.005 | 0.003 | .17 | <.01 |
| Drinks/day | 0.056 | 0.042 | .18 | <.01 |
| Years Worked | - 0.008 | 0.005 | .12 | <.01 |
| Triglycerides* | 0.201 | 0.062 | .001 | .02 |

$R^2 = .07$
Adj $R^2 = .05$
*Natural log

Table 67

Multivariable Regression Model of T4* by PFOS
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 2.263 | 0.090 | < .001 | - |
| PFOS | - 0.003 | 0.009 | .78 | < .01 |
| Production Job (yes/no) | - 0.003 | 0.022 | .91 | < .01 |
| Antwerp/Decatur | 0.011 | 0.024 | .64 | < .01 |
| Age | - 0.003 | 0.002 | .08 | < .01 |
| BMI | 0.001 | 0.003 | .66 | < .01 |
| Cigarettes/day | 0.0009 | 0.0009 | .32 | < .01 |
| Drinks/day | - 0.024 | 0.012 | .04 | < .01 |
| Years Worked | 0.001 | 0.001 | .35 | < .01 |
| Triglycerides* | - 0.018 | 0.017 | .29 | < .01 |

$R^2$ = .02
Adj $R^2$ = .01
*Natural log

Table 68

Multivariable Regression Model of T4* by PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 2.263 | 0.090 | < .0001 | - |
| PFOA | 0.0003 | 0.007 | .97 | <.01 |
| Production Job (yes/no) | - 0.005 | 0.023 | .82 | <.01 |
| Antwerp/Decatur | 0.010 | 0.024 | .69 | <.01 |
| Age | - 0.003 | 0.002 | .09 | <.01 |
| BMI | 0.001 | 0.003 | .64 | <.01 |
| Cigarettes/day | 0.001 | 0.0009 | .31 | <.01 |
| Drinks/day | -0.02 | 0.01 | .04 | <.01 |
| Years Worked | 0.001 | 0.001 | .37 | <.01 |
| Triglycerides* | - 0.019 | 0.017 | .28 | <.01 |

$R^2 = .03$
Adj $R^2 = .01$
*Natural log

Table 69

Multivariable Regression Model of T4* by PFOS and PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 2.263 | 0.090 | < .0001 | - |
| PFOS | - 0.003 | 0.010 | .74 | < .01 |
| PFOA | 0.001 | 0.008 | .86 | < .01 |
| Production Job (yes/no) | - 0.004 | 0.023 | .87 | < .01 |
| Antwerp/Decatur | 0.010 | 0.024 | .68 | < .01 |
| Age | - 0.003 | 0.002 | .09 | < .01 |
| BMI | 0.001 | 0.003 | .65 | < .01 |
| Cigarettes/day | 0.0009 | 0.0009 | .32 | < .01 |
| Drinks/day | - 0.024 | 0.012 | .04 | < .01 |
| Years Worked | 0.001 | 0.001 | .35 | < .01 |
| Triglycerides* | - 0.018 | 0.017 | .29 | < .01 |

$R^2 = .03$
Adj $R^2 = < .01$
*Natural log

Table 70

Multivariable Regression Model of T4* by TOF
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 2.263 | 0.090 | < .0001 | - |
| TOF | 0.0002 | 0.006 | .97 | < .01 |
| Production Job (yes/no) | - 0.005 | 0.023 | .82 | < .01 |
| Antwerp/Decatur | 0.010 | 0.024 | .68 | < .01 |
| Age | - 0.003 | 0.002 | .09 | < .01 |
| BMI | 0.001 | 0.003 | .64 | < .01 |
| Cigarettes/day | 0.001 | 0.0009 | .31 | < .01 |
| Drinks/day | - 0.024 | 0.012 | .04 | < .01 |
| Years Worked | 0.001 | 0.001 | .37 | < .01 |
| Triglycerides* | - 0.019 | 0.017 | .28 | < .01 |

$R^2 = .03$
Adj $R^2 = < .01$
*Natural log

Table 71

Multivariable Regression Model of Free T4* by PFOS
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

|  | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 0.299 | 0.076 | <.0001 | - |
| PFOS | -0.004 | 0.008 | .63 | <.01 |
| Production Job (yes/no) | -0.030 | 0.019 | .11 | <.01 |
| Antwerp/Decatur | -0.021 | 0.020 | .28 | .03 |
| Age | -0.003 | 0.001 | .03 | .01 |
| BMI | -0.003 | 0.002 | .13 | <.01 |
| Cigarettes/day | -0.0009 | 0.0008 | .27 | <.01 |
| Drinks/day | 0.006 | 0.010 | .56 | <.01 |
| Years Worked | 0.002 | 0.001 | .21 | <.01 |
| Triglycerides* | 0.003 | 0.014 | .85 | <.01 |

$R^2 = .06$
Adj $R^2 = .04$
*Natural log

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Table 72

Multivariable Regression Model of Free T4* by PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 0.299 | 0.076 | .0001 | - |
| PFOA | - 0.006 | 0.006 | .31 | .01 |
| Production Job (yes/no) | - 0.025 | 0.019 | .19 | <.01 |
| Antwerp/Decatur | - 0.017 | 0.021 | .41 | .02 |
| Age. | - 0.003 | 0.001 | .02 | .01 |
| BMI | - 0.003 | 0.002 | .13 | <.01 |
| Cigarettes/day | - 0.0009 | 0.0008 | .27 | <.01 |
| Drinks/day | 0.006 | 0.010 | .53 | <.01 |
| Years Worked | 0.002 | 0.001 | .20 | <.01 |
| Triglycerides* | 0.004 | 0.014 | .78 | <.01 |

$R^2 = .07$
Adj $R^2 = .04$
*Natural log

Table 73

Multivariable Regression Model of Free T4* by PFOS and PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 0.299 | 0.076 | .0001 | - |
| PFOS | -0.0005 | 0.008 | .96 | <.01 |
| PFOA | -0.006 | 0.007 | .37 | <.01 |
| Production Job (yes/no) | -0.025 | 0.020 | .21 | <.01 |
| Antwerp/Decatur | -0.020 | 0.210 | .41 | .02 |
| Age | -0.003 | 0.001 | .02 | .01 |
| BMI | -0.003 | 0.002 | .13 | <.01 |
| Cigarettes/day | -0.0009 | 0.0008 | .27 | .002 |
| Drinks/day | 0.006 | 0.010 | .54 | <.01 |
| Years Worked | 0.002 | 0.001 | .20 | <.01 |
| Triglycerides* | 0.004 | 0.014 | .77 | <.01 |

$R^2 = .07$
Adj $R^2 = .04$
*Natural log

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Table 74

Multivariable Regression Model of Free T4* by TOF
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 0.299 | 0.076 | .0001 | - |
| TOF | - 0.004 | 0.005 | .37 | .01 |
| Production Job (yes/no) | - 0.025 | 0.020 | .19 | <.01 |
| Antwerp/Decatur | - 0.018 | 0.020 | .38 | .02 |
| Age | - 0.003 | 0.001 | .02 | .01 |
| BMI | - 0.003 | 0.002 | .13 | <.01 |
| Cigarettes/day | - 0.0009 | 0.0008 | .27 | <.01 |
| Drinks/day | 0.006 | 0.010 | .01 | <.01 |
| Years Worked | 0.002 | 0.001 | .19 | <.01 |
| Triglycerides* | 0.004 | 0.014 | .79 | <.01 |

$R^2 = .06$
Adj $R^2 = .04$
*Natural log

Table 75

Multivariable Regression Model of THBR* by PFOS
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

|  | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 3.589 | 0.041 | <.0001 | - |
| PFOS | - 0.003 | 0.004 | .40 | .03 |
| Production Job (yes/no) | - 0.006 | 0.010 | .55 | <.01 |
| Antwerp/Decatur | - 0.090 | 0.011 | <.0001 | .30 |
| Age | - 0.0005 | 0.0008 | .50 | <.01 |
| BMI | - 0.001 | 0.001 | .29 | <.01 |
| Cigarettes/day | - 0.0007 | 0.0004 | .13 | <.01 |
| Drinks/day | - 0.015 | 0.005 | .005 | .01 |
| Years Worked | - 0.0002 | 0.0007 | .77 | <.01 |
| Triglycerides* | - 0.003 | 0.008 | .75 | <.01 |

$R^2 = .35$
Adj $R^2 = .34$
*Natural log

Table 76

Multivariable Regression Model of THBR* by PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 3.589 | 0.041 | < .0001 | -- |
| PFOA | - 0.003 | 0.003 | .43 | .04 |
| Production Job (yes/no) | - 0.006 | 0.010 | .58 | < .01 |
| Antwerp/Decatur | - 0.089 | 0.011 | < .0001 | .28 |
| Age | - 0.0005 | 0.0008 | .48 | < .01 |
| BMI | - 0.001 | 0.001 | .29 | < .01 |
| Cigarettes/day | - 0.0007 | 0.0004 | .13 | < .01 |
| Drinks/day | 0.015 | 0.005 | .004 | .01 |
| Years Worked | - 0.0002 | 0.0006 | .71 | < .01 |
| Triglycerides* | - 0.002 | 0.008 | .76 | < .01 |

$R^2 = .35$
Adj $R^2 = .34$
*Natural log

Table 77

Multivariable Regression Model of THBR* by PFOS and PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial R² |
|---|---|---|---|---|
| Intercept | 3.589 | 0.041 | <.0001 | - |
| PFOS | -0.003 | 0.005 | .58 | .03 |
| PFOA | -0.002 | 0.004 | .64 | .02 |
| Production Job (yes/no) | -0.005 | 0.011 | .66 | <.01 |
| Antwerp/Decatur | -0.088 | 0.011 | <.0001 | .28 |
| Age | -0.0006 | 0.0008 | .47 | <.01 |
| BMI | -0.001 | 0.001 | .28 | <.01 |
| Cigarettes/day | -0.0007 | 0.0004 | .13 | <.01 |
| Drinks/day | 0.015 | 0.005 | .004 | .01 |
| Years Worked | -0.0002 | 0.0007 | .78 | <.01 |
| Triglycerides* | -0.002 | 0.008 | .79 | <.01 |

R² = .35
Adj R² = .34
*Natural log

000240

Table 78

Multivariable Regression Model of THBR* by TOF
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 3.589 | 0.041 | <.0001 | - |
| TOF | - 0.003 | 0.003 | .29 | .05 |
| Production Job (yes/no) | - 0.004 | 0.011 | .69 | <.01 |
| Antwerp/Decatur | - 0.088 | 0.011 | <.0001 | .28 |
| Age | - 0.0006 | 0.0008 | .45 | <.01 |
| BMI | - 0.001 | 0.001 | .28 | <.01 |
| Cigarettes/day | - 0.0007 | 0.0004 | .13 | <.01 |
| Drinks/day | 0.015 | 0.005 | .004 | .01 |
| Years Worked | - 0.0002 | 0.0007 | .77 | <.01 |
| Triglycerides* | - 0.002 | 0.008 | .80 | <.01 |

$R^2 = .35$
Adj $R^2 = .34$
*Natural log

Table 79

Multivariable Regression Model of FTI* by PFOS
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 1.239 | 0.085 | <.0001 | - |
| PFOS | -0.006 | 0.009 | .45 | .01 |
| Production Job (yes/no) | -0.009 | 0.021 | .65 | <.01 |
| Antwerp/Decatur | -0.078 | 0.022 | .0004 | .07 |
| Age | -0.003 | 0.002 | .03 | .02 |
| BMI | -0.0001 | 0.002 | .96 | <.01 |
| Cigarettes/day | 0.0002 | 0.0009 | .82 | <.01 |
| Drinks/day | -0.008 | 0.011 | .44 | <.01 |
| Years Worked | 0.001 | 0.001 | .41 | <.01 |
| Triglycerides¹ | 0.033 | 0.006 | .16 | .01 |

R² = .10
Adj R² = .08
*Natural log

Table 80

Multivariable Regression Model of FTI* by PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 1.239 | 0.085 | <.0001 | - |
| PFOA | - 0.002 | 0.007 | .77 | .01 |
| Production Job (yes/no) | - 0.012 | 0.021 | .56 | <.01 |
| Antwerp/Decatur | - 0.079 | 0.023 | .0006 | .07 |
| Age | - 0.003 | 0.002 | .03 | .02 |
| BMI | - 0.00007 | 0.002 | .98 | <.01 |
| Cigarettes/day | 0.0002 | 0.0009 | .80 | <.01 |
| Drinks/day | - 0.008 | 0.011 | .44 | <.01 |
| Years Worked | 0.001 | 0.001 | .47 | <.01 |
| Triglycerides* | - 0.023 | 0.016 | .15 | <.01 |

$R^2 = .10$
Adj $R^2 = .08$
*Natural log

Table 81

Multivariable Regression Model of FTI* by PFOS and PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 1.239 | 0.085 | < .0001 | - |
| PFOS | - 0.006 | 0.009 | .49 | .01 |
| PFOA | 0.0002 | 0.008 | .98 | < .01 |
| Production Job (yes/no) | - 0.010 | 0.022 | .66 | < .01 |
| Antwerp/Decatur | - 0.079 | 0.023 | .0007 | .06 |
| Age | - 0.003 | 0.002 | .03 | .02 |
| BMI | - 0.0001 | 0.002 | .96 | .02 |
| Cigarettes/day | 0.0002 | 0.0009 | .82 | < .01 |
| Drinks/day | - 0.008 | 0.011 | .44 | < .01 |
| Years Worked | 0.001 | 0.001 | .41 | .002 |
| Triglycerides* | - 0.022 | 0.016 | .17 | .004 |

$R^2 = .10$
Adj $R^2 = .08$
*Natural log

000244

Table 82

## Multivariable Regression Model of FTI* by TOF
## and Other Potential Explanatory Variables
## for Antwerp and Decatur Male Employee Participants,
## 2000 Medical Surveillance Program

|  | Parameter | SE | p value | Partial R² |
|---|---|---|---|---|
| Intercept | 1.239 | 0.085 | <.0001 | - |
| TOF | -0.003 | 0.006 | .62 | .01 |
| Production Job (yes/no) | -0.010 | 0.022 | .63 | <.01 |
| Antwerp/Decatur | -0.078 | 0.023 | .0007 | .06 |
| Age | -0.003 | 0.002 | .03 | .02 |
| BMI | -0.0001 | 0.002 | .97 | <.01 |
| Cigarettes/day | 0.0002 | 0.0009 | .81 | <.01 |
| Drinks/day | -0.008 | 0.011 | .44 | <.01 |
| Years Worked | 0.001 | 0.001 | .44 | <.01 |
| Triglycerides* | -0.022 | 0.016 | .16 | <.01 |

R² = .10
Adj R² = .08
*Natural log

Table 83

Multivariable Regression Model of T3* by PFOS
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial R$^2$ |
|---|---|---|---|---|
| Intercept | 4.702 | 0.074 | <.0001 | - |
| PFOS | 0.015 | 0.007 | .04 | .01 |
| Production Job (yes/no) | 0.022 | 0.018 | .23 | .01 |
| Antwerp/Decatur | -0.099 | 0.019 | <.0001 | .03 |
| Age | -0.002 | 0.001 | .24 | <.01 |
| BMI | 0.005 | 0.002 | .02 | .02 |
| Cigarettes/day | 0.003 | 0.0008 | .001 | .02 |
| Drinks/day | -0.027 | 0.009 | .004 | .02 |
| Years Worked | -0.0006 | 0.001 | .60 | <.01 |
| Triglycerides* | 0.020 | 0.014 | .15 | <.01 |

R$^2$ = .12
Adj R$^2$ = .10
*Natural log

Table 84

Multivariable Regression Model of T3* by PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

|  | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 4.702 | 0.073 | <.0001 | - |
| PFOA | 0.016 | 0.006 | .01 | .02 |
| Production Job (yes/no) | 0.015 | 0.019 | .41 | <.01 |
| Antwerp/Decatur | -0.109 | 0.020 | <.0001 | .03 |
| Age | -0.001 | 0.001 | .33 | <.01 |
| BMI | 0.005 | 0.002 | .02 | .02 |
| Cigarettes/day | 0.003 | 0.0008 | .001 | .02 |
| Drinks/day | -0.028 | 0.009 | .003 | .02 |
| Years Worked | -0.0004 | 0.001 | .70 | <.01 |
| Triglycerides* | 0.018 | 0.014 | .20 | <.01 |

$R^2 = .13$
Adj $R^2 = .11$
*Natural log

Table 85

Multivariable Regression Model of T3* by PFOS and PFOA
and Other Potential Explanatory Variables
for Antwerp and Decatur Male Employee Participants,
2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 4.703 | 0.073 | <.0001 | - |
| PFOS | 0.009 | 0.008 | .29 | .01 |
| PFOA | 0.013 | 0.007 | .05 | <.01 |
| Production Job (yes/no) | 0.012 | 0.019 | .54 | <.01 |
| Antwerp/Decatur | -0.109 | 0.020 | <.0001 | .03 |
| Age | -0.001 | 0.001 | .35 | <.01 |
| BMI | 0.005 | 0.002 | .01 | .02 |
| Cigarettes/day | 0.003 | 0.0008 | .001 | .02 |
| Drinks/day | -0.028 | 0.009 | .003 | .02 |
| Years Worked | -0.0006 | 0.001 | .59 | <.01 |
| Triglycerides* | 0.017 | 0.014 | .23 | <.01 |

$R^2$ = .13
Adj $R^2$ = .11
*Natural log

Table 86

## Multivariable Regression Model of T3* by TOF and Other Potential Explanatory Variables for Antwerp and Decatur Male Employee Participants, 2000 Medical Surveillance Program

| | Parameter | SE | p value | Partial $R^2$ |
|---|---|---|---|---|
| Intercept | 4.702 | 0.073 | < .0001 | - |
| TOF | 0.014 | 0.005 | .004 | .02 |
| Production Job (yes/no) | 0.011 | 0.019 | .54 | < .01 |
| Antwerp/Decatur | - 0.109 | 0.020 | < .0001 | .03 |
| Age | - 0.001 | 0.001 | .35 | < .01 |
| BMI | 0.005 | 0.002 | .01 | .02 |
| Cigarettes/day | 0.003 | 0.0007 | .001 | .02 |
| Drinks/day | - 0.028 | 0.009 | .003 | .02 |
| Years Worked | - 0.0007 | 0.001 | .56 | < .01 |
| Triglycerides* | 0.017 | 0.014 | .22 | < .01 |

$R^2$ = .13
Adj $R^2$ = .11
*Natural log

Figure 1. Linear Regression Model of Triglgycerides* by PFOA* for Antwerp
Male Employees, 2000 Medical Surveillance Program
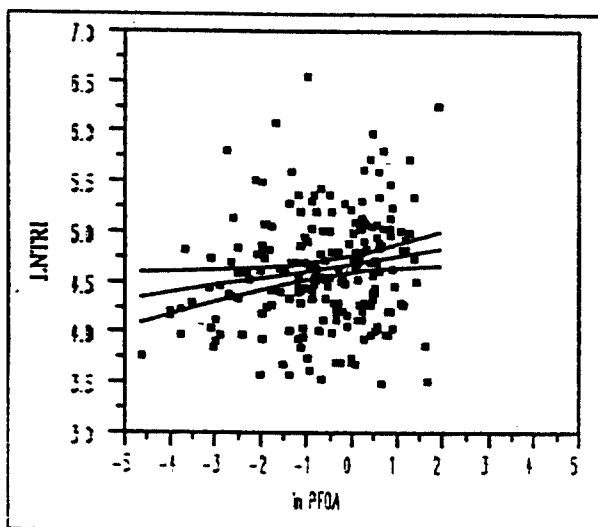


## Summary of Fit

RSquare                                    0.029

## Analysis of Variance

| Source | DF | Sum of Squares | Mean Square | F Ratio |
|--------|-----|----------------|-------------|---------|
| Model  | 1   | 1.863          | 1.863       | 6.211   |
| Error  | 204 | 61.193         | 0.299       | Prob>F  |
| C Total| 205 | 63.056         |             | 0.014   |

## Parameter Estimates

| Term | Estimate | Std Error | t Ratio | Prob>|t| |
|------|----------|-----------|---------|----------|
| Intercept | 4.695 | 0.042 | 111.43 | <.0001 |
| ln PFOA   | 0.073 | 0.029 | 2.49   | 0.014  |

*natural log

## Figure 2. Linear Regression of Triglycerides* by PFOA* for Decatur Male Employees, 2000 Medical Surveillance Program
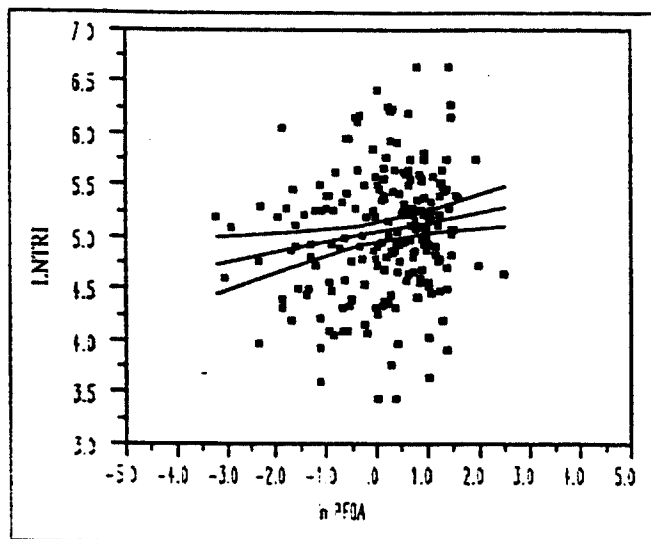


### Summary of Fit

RSquare                                    0.028

### Analysis of Variance

| Source | DF | Sum of Squares | Mean Square | F Ratio |
|--------|----|----------------|-------------|---------|
| Model | 1 | 2.164 | 2.164 | 6.232 |
| Error | 213 | 73.969 | 0.347 | Prob>F |
| C Total | 214 | 76.133 | | 0.013 |

### Parameter Estimates

| Term | Estimate | Std Error | t Ratio | Prob>|t| |
|------|----------|-----------|---------|----------|
| Intercept | 5.052 | 0.041 | 122.27 | <.0001 |
| ln PFOA | 0.098 | 0.039 | 2.50 | 0.013 |

*natural log

## Figure 3. Linear Regression of Triglycerides* by PFOA* for Antwerp and Dec_____  Female Employees, 2000 Medical Surveillance Program
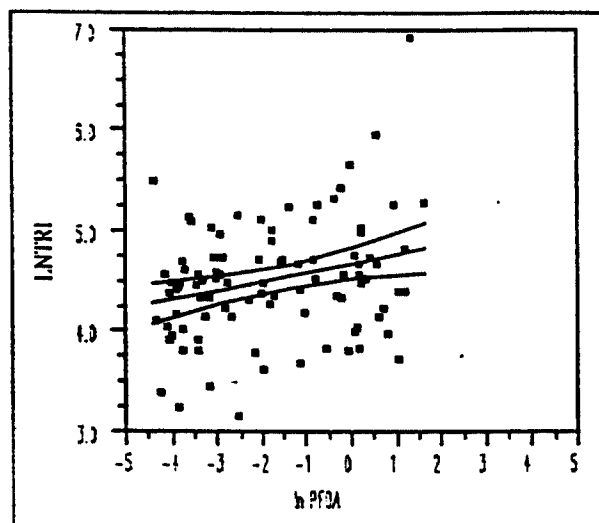


## Summary of Fit

RSquare 0.078

## Analysis of Variance

| Source | DF | Sum of Squares | Mean Square | F Ratio |
|--------|-----|----------------|-------------|---------|
| Model | 1 | 2.519 | 2.519 | 8.010 |
| Error | 95 | 29.877 | 0.314 | Prob>F |
| C Total | 96 | 32.396 | | 0.006 |

## Parameter Estimates

| Term | Estimate | Std Error | t Ratio | Prob>|t| |
|------|----------|-----------|---------|----------|
| Intercept | 4.690 | 0.081 | 58.14 | <.0001 |
| ln PFOA | 0.091 | 0.032 | 2.83 | 0.006 |

*natural log

Figure 4. Linear Regression of Triglycerides* by PFOA* for Cottage Grove Male Employees, 2000 Medical Surveillance Program
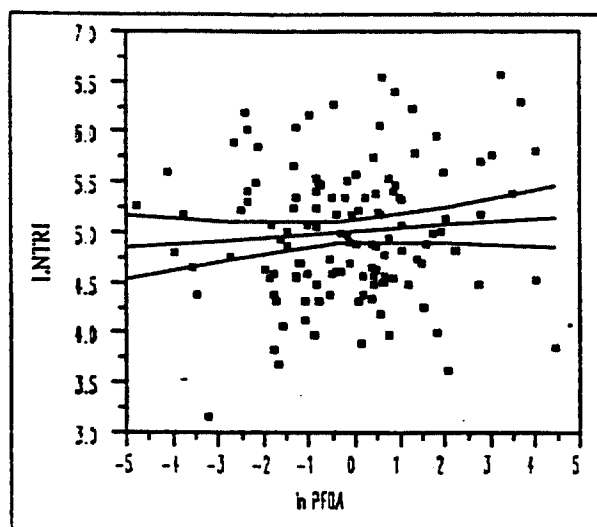


## Summary of Fit

| RSquare | 0.008 |
|---|---|

## Analysis of Variance

| Source | DF | Sum of Squares | Mean Square | F Ratio |
|---|---|---|---|---|
| Model | 1 | 0.452 | 0.452 | 1.076 |
| Error | 129 | 54.251 | 0.421 | Prob>F |
| C Total | 130 | 54.704 | | 0.302 |

## Parameter Estimates

| Term | Estimate | Std Error | t Ratio | Prob>|t| |
|---|---|---|---|---|
| Intercept | 5.022 | 0.057 | 88.04 | <.0001 |
| ln PFOA | 0.032 | 0.031 | 1.04 | 0.302 |

*natural log

# FINAL REPORT
## Epidemiology, 220-3W-05
## Medical Department
## 3M Company
## St. Paul, MN 55144

Date: October 11, 2001*

Title: A Longitudinal Analysis of Serum Perfluorooctanesulfonate (PFOS) and Perfluorooctanoate (PFOA) Levels in Relation to Lipid and Hepatic Clinical Chemistry Test Results from Male Employee Participants of the 1994/95, 1997 and 2000 Fluorochemical Medical Surveillance Program

| | |
|---|---|
| Study | Protocol Number (not applicable) |
| Start Date: July 1, 2001 | IRB Approval |
| | Exempt   Expedited |
| | X |

IRB Approval Date: (not applicable as these data are from a medical surveillance program)

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* (Corrections made from previous version)

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## ABSTRACT

The 3M fluorochemical medical surveillance program was conducted in 1994/95, 1997 and 2000 at the company's Antwerp (Belgium) and Decatur (Alabama) manufacturing plants. Although cross-sectional assessments of the data have been reported, the opportunity to conduct a longitudinal assessment became possible as a result of a large number of employee participants in the 2000 fluorochemical medical surveillance program. A total of 175 male employees voluntarily participated in the 2000 program and at least one of the two previous program years. A total of 106 (61 percent) of the 175 employees participated in the 1994/95 program and 110 (63 percent) of the 175 participated in the 1997 program. Of these 175 employees, a total of 41 (24 percent) participated in all three years (Antwerp = 21, Decatur = 20), 65 (37 percent) participated in 1994/95 and 2000 (Antwerp = 45, Decatur = 20) and 69 (39 percent) participated in 1997 and 2000 (Antwerp = 34, Decatur = 35). There were insufficient number of female employees to conduct any meaningful longitudinal assessment. Only 14 female employees participated in the 2000 fluorochemical medical surveillance program and at least one of the previous program years.

Serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) were assayed in each surveillance program year although the method of analysis (high performance liquid chromatography mass spectrometry) differed slightly between years. A different research laboratory was used to assay PFOS and PFOA in each year.

The same hospital laboratory analyzed the clinical chemistries for all three surveillance years. These included: cholesterol (mg/dl), high density lipoproteins (HDL,

mg/dl) and triglycerides (mg/dl); alkaline phosphatase (IU/L), gamma glutamyl transferase (GGT, IU/L), aspartate aminotransferase (AST, IU/L), alanine aminotransferase (ALT, IU/L), total and direct bilirubin (mg/dl). Most reference ranges remained relatively constant over time except for ALT. In each surveillance year, potential confounding factors were also determined. These covariates included age, body mass index, number of alcoholic drinks per day and cigarettes smoked per day.

The continuous outcomes of lipid and hepatic clinical chemistry tests were evaluated as repeated measures incorporating the random subject effect fitted to a mixed model by the MIXED procedure in the SAS statistical package. Restricted maximum likelihood estimates of variance parameters were computed. Adjusted regression models were built by introducing all covariates and testing the covariance structure. Significant coefficients were defined when the p value was < .05.

There was a positive association between PFOA and serum cholesterol and triglycerides over time but not with PFOS. This was association was limited to the Antwerp employees and, in particular, the 21 Antwerp employees who participated in all three surveillance years. This positive association between PFOA and serum lipids is opposite the inconsistent toxicological evidence that suggested a possible hypolipidemic effect of PFOA in rodents and no effect in primates. Adjusting for potential confounders, there were no temporal changes associated with the fluorochemical tests, PFOS, PFOA and TOF, and the hepatic clinical chemistry tests.

Limitations of this study included the number of employees with three years of surveillance data (only 24% of the 175 subjects), the inability to analyze temporal changes due to small numbers in female employees, the use of different laboratories and

the associated systematic (experimental error) with each fluorochemical assay for the

three surveillance program years and the lower levels of serum PFOS and PFOA

measured in each program year among these employees compared with those that cause

effects in laboratory animals.

## INTRODUCTION

The 3M fluorochemical medical surveillance program is conducted on a routine basis at the company's Antwerp (Belgium) and Decatur (Alabama) manufacturing plants. Employee participation is voluntary. Prior to 1994, only total organic fluorine was measured and no specific fluorochemical analytes were measured. Serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) have been routinely assayed since 1994/95 rather than total organic fluorine as the analytical capabilities have improved. Cross-sectional analyses of the 1994/95 and 1997 medical surveillance program data and the 2000 data in relation to Antwerp and Decatur employees' serum PFOS levels have been reported elsewhere (Olsen et al, 1999a, 1999b, 2001). In the 1994/1995 medical surveillance program, a total of 178 male employees participated (Antwerp = 88; Decatur = 90) and 149 male employees participated in the 1997 program (Antwerp = 65; Decatur = 84). For these two program years, there were too few female participants to include in the data analysis (Olsen et al 1998). In the 2000 fluorochemical medical surveillance program. there were considerably more participants: 421 males (Antwerp = 206; Decatur = 215) and 97 females (Antwerp = 49; Decatur = 48). It was suspected that the increased voluntary participation in 2000 was due to increased employee awareness of the persistence and prevalence of PFOS in human tissue and the environment and the company's May 16, 2000 phase out announcement that it would cease the production of perfluorooctanyl chemistry in certain repellents and surfactants by the end of 2000.

Regardless of the surveillance year, there have been several consistent differences between the Antwerp and Decatur male employee populations. The Antwerp male

employee population has been significantly younger than Decatur, has had lower Body Mass Indices (BMI) and higher self-reported daily consumption of alcohol. In addition, the Antwerp male employee population clinical chemistry profiles were different for several tests including lower mean alkaline phosphatase and triglyceride values and higher total bilirubin and HDL values than the Decatur male employee population. Analyses of workers' lipid and hepatic clinical chemistry results have not been associated with hypolipidemic effects and PFOS as reported in rodents (3M Company 2000; Haughom and Spydevold 1992; Ikeda et al 1987; Pastoor et al 1987; Seacat et al 2001a; Sohlenius et al 1993) and primates (Seacat et al 2001b). In the 2000 medical surveillance program, statistical analyses also examined the relation between PFOA and a calculated total organic fluorine index (TOF) to clinical chemistries, hematology, thyroid hormones and urinalyses (Olsen et al 2001). A positive association was observed between triglycerides and PFOA; however, this association was opposite the data that have inconsistently reported a hypolipidemia effect of PFOA in rodents (Haughom and Spydevold 1992; Pastoor et al 1987) and no effect in primates (Butenhoff et al 2001). Furthermore, this positive association between PFOA and triglycerides has not been observed at the 3M Cottage Grove manufacturing plant (Olsen et al 2000) where employees' serum levels have, historically, been much higher than those measured among Antwerp and Decatur employees (Olsen et al 1999; 2001a; Olsen et al 2001b).

The inability to assess temporal changes in cross-sectional studies is a well-known limitation of this design. The large participation of employees in the 2000 fluorochemical medical surveillance who may have participated in the 1994/95 and/or 1997 surveillance programs at these two manufacturing sites allowed for an opportunity

to conduct a longitudinal analysis among the male employee population. Altogether, a total of 175 employees (Antwerp = 100; Decatur = 75) who participated in 2000 had also participated in at least one previous fluorochemical medical surveillance exam since 1994/95. Therefore, the purpose of this analysis was to conduct a longitudinal assessment of this 6 year time period regarding the relationship of PFOS, PFOA and TOF to the medical surveillance data collected on these 175 Antwerp and Decatur male employees.

## METHODS

### Data Collection

Data were compiled from the 1994/95, 1997 and 2000 fluorochemical medical surveillance program databases. A total of 175 male employees participated in the 2000 program and at least one of the two previous program years. A total of 106 (61 percent) of the 175 employees participated in the 1994/95 program and 110 (63 percent) of the 175 participated in the 1997 program. Of these 175 employees, a total of 41 (24 percent) participated in all three years (Antwerp = 21, Decatur = 20), 65 (37 percent) participated in 1994/95 and 2000 (Antwerp = 45, Decatur = 20) and 69 (39 percent) participated in 1997 and 2000 (Antwerp = 34, Decatur = 35). For purposes of brevity, these three subpopulations will hereafter be referred to as subcohorts A, B and C.

Demographic data (age, BMI, alcoholic drinks per day and cigarettes per day) were recorded for each employee in each surveillance year. A standard set of clinical chemistries and hematology data was also obtained for each employee. Given results from previous toxicological studies, the longitudinal analyses focused on lipid

[cholesterol (mg/dl), high density lipoproteins (HDL, mg/dl) and triglycerides (mg/dl)] and hepatic [alkaline phosphatase (IU/L), gamma glutamyl transferase (GGT, IU/L), aspartate aminotransferase (AST, IU/L), alanine aminotransferase (ALT, IU/L), total and direct bilirubin (mg/dl)] clinical chemistries that were measured in each program year by the same laboratory (Allina Laboratories, St. Paul , MN).  Reference ranges were relatively constant over time, although for ALT the range declined from 20-65 IU/L in 1994/95 to 1-40 IU/L in 1997 and 2000.

Fluorochemical Analyses

PFOS and PFOA were assayed in 1994/95, 1997 and 2000.  However, the method of analysis differed slightly for each year.  In 1994/95, the method used tetrabutylammonium to ion-pair with PFOS and PFOA in the serum (Johnson et al 1996). The ion-pairs were then extracted with ethyl acetate.  The abstraction product was then analyzed using high-performance liquid chromatograph-thermospray mass spectrometry. In 1997, the serum samples were analyzed by liquid chromatography/mass spectrometry, using selected ion monitoring in the negative-ion mode (Anderson and Mulvanna 1997a; 1997b).  In 2000, sera samples were extracted using an ion-pairing extraction procedure (Hansen et al, 2001).  Only in 2000 were the extracts quantitatively analyzed for PFOS and PFOA as well as the other analytes: PFHS (perfluorohexanesulfonate), PFOSAA (N-ethyl perfluorooctanesulfonamidoacetate), M570 (N-methyl perfluorooctanesulfonamidoacetate), PFOSA (perfluorooctanesulfonateamide) and M556 (perfluorooctanesulfonamidoacetate).  High-performance liquid chromatography/electrospray tandem mass spectrometry (HPLC/ESMSMS) was the

technique used in 2000. The samples were evaluated versus an extracted curve from a human serum matrix. Analyses were conducted at different laboratories in the three surveillance years. For purposes of this longitudinal analysis, a total organic fluorine index (TOF) was determined by calculating the percent of PFOS and PFOA that was attributed to organic fluorine (64.7 and 69.0 percent, respectively) multiplied by the ppm measured for each of these two fluorochemicals and then summed to produce the TOF.

## Data Analysis

Briefly, mixed models can be used in the analysis of repeated measures data which are simply data sets with multiple measurements of a response variable on the same subject over time. Detailed explanation of these models is provided elsewhere (Littell 1996; 2000). Mixed models contain factor effects which are considered both fixed and random. An effect is fixed if the levels in the study represent all possible levels of the factor, or at least all levels about which inference is to be made. Factor effects are random if the levels of the factor that are used in the study represent only a random sample of a larger set of potential levels.

The focus of the standard linear model is to model the mean of y by using the fixed-effects parameters $\beta$. That is,

$$y = X\beta + \epsilon$$

where y represents a vector of observed data, $\beta$ is an unknown vector of fixed effects parameters with known design matrix $X$, and $\epsilon$ is an unknown random error vector modeling the statistical 'noise' around $X\beta$. The residual errors $\epsilon$ are assumed to be

independent and identically distributed Gaussian random variables with mean 0 and variance $\sigma^2$.

A generalized standard linear model is a mixed model which is:

$$y = X\beta + Z\gamma + \epsilon$$

where $\gamma$ is an unknown vector of random-effects parameters with known design matrix $Z$, and $\epsilon$ is an unknown random error vector whose elements are no longer required to be independent and homogeneous. If $\gamma + \epsilon$ are assumed to be Gaussian random variables that are uncorrelated and have expectations $0$ and variances $G$ and $R$, respectively, then the variance of $y$ is:

$$V = ZGZ' + R$$

The variance of the data, $y$, can be modeled by specifying the structure of $Z$, $G$ and $R$. The model matrix $Z$ is designed in the same fashion as $X$, the model matrix for the fixed-effects parameters.

For the matrices $G$ and $R$, a covariance structure must be selected in using mixed models. Since observations on different subjects are assumed to be independent, the structure refers to the covariance pattern of repeated measurements on the same subject. For most of these structures, the covariance between two observations on the same subject depends only on the length of the time interval between measurements and the variance is constant over time. Numerous covariance structures exist. Common examples include the following. Simple covariance structure (SIM) specifies that the observations are independent, even on the same subject, and have homogeneous variance. It is usually not realistic for most repeated measures data because it specifies that observations on the same subject are independent. Compound symmetric (CS, otherwise

known as variance components) structure specifies that observations on the same subject have homogeneous covariance and homogeneous variance. Correlations between two observations are equal for all pairs of observations on the same subject. Autoregressive order 1 (AR(1))covariance structure specifies homogeneous variance but that covariances between observations on the same subject are not equal, but decrease toward zero with increasing time interval between measurements (lag). Its limitation is that observations on the same subject far apart in time would be essentially independent. Autoregressive with random effect for subject (AR + RE) covariance structure specifies homogeneous variance plus the covariance between observations on the same subject arises from two sources: 1) any two observations share a common contribution because they are on the same subject; and 2) the covariance between observations decreases exponentially with lag but only to the common contribution (not to independence). Toeplitz (TOEP) structure specifies that covariance depends only on lag but not as a mathematical function with a small number of parameters. The 'unstructured' structure (UN) specifies no patterns in the covariance matrix and is therefore completely general. The above structures are appropriate if equal spacing (of data) is assumed in a time series analyses. In situations where unequally spaced longitudinal measurements exist, spatial covariance structures can be used. In the present analyses, equal spacing was assumed given there were approximately 3 years between each medical surveillance program examinations.

Akaike's information criterion (AIC) and Schwarz's Bayesian criterion (SBC) are indices of relative goodness-of-fit that were used to compare models with the same fixed effects, but different covariance structures. SBC penalizes models more severely for the

number of estimated parameters than AIC and thus the two criteria did not always agree on the choice of 'best' model. SBC was preferred.

In the present study, the continuous outcomes of lipid and hepatic clinical chemistry tests were evaluated as repeated measures incorporating the random subject effect fitted to a mixed model by the MIXED procedure in the SAS statistical package (Littell et al 1996). Restricted maximum likelihood estimates (REML) of variance parameters were computed. Adjusted regression models were built by introducing all covariates (see below) and testing the covariance structure. Based on goodness-of-fit tests described above, AR+RE, was routinely considered the best covariance structure chosen for the mixed models. Covariates included PFOS (or PFOA or TOF), years of observation, the interaction term of PFOS and years of observation, age, body mass index (BMI), cigarettes smoked per day, alcohol drinks per day, year at first entry and baseline (at first observation) years worked. For hepatic clinical chemistry tests, serum triglycerides was also considered a covariate (Olsen et al 2001a).

RESULTS

Provided in Table 1 are cross-sectional analyses of the study subjects who participated in each of the three years (1994/95, 1997 and 2000) stratified by location. As reported previously in the complete cross-sectional analyses of these programs (Olsen et al 1998; 1999; 2001), Antwerp employees in this longitudinal investigation were younger, had lower BMIs and drank more alcoholic beverages than Decatur employees. They also had consistently lower triglyceride and alkaline phosphatase levels and higher HDL and total bilirubin levels. Decatur employees, on average, had serum PFOS levels

that were higher by approximately 0.5 ppm in each cross-sectional analysis. Similar findings were observed for PFOA except with the 1997 data where the two populations had comparable mean PFOA levels.

Provided in the following two tables are the cross-sectional analyses for the three subcohorts by location. Among Antwerp employees (Table 2), each of the three subcohorts had lower mean serum PFOS levels in 2000 than at their year of entry whereas there were no consistent changes across subcohorts with PFOA. Among the three Decatur subcohorts (Table 3) mean PFOS values declined over time but mean PFOA levels tended to increase.

Provided in tables 4 through 30 are the mixed model coefficient estimates, standard errors, p-values and 95% confidence intervals from testing potential determinants of lipid and hepatic clinical chemistry change. The natural log was used for all dependent variables.

Tables 4 through 6 contain the analyses for cholesterol. There was no change in cholesterol associated with PFOS (Table 4). Overall, PFOA was positively associated with cholesterol as the main effect coefficient was significantly positive but its interaction with time (years variable) was negative (Table 5). Provided in Tables 5A through 5D are separate analyses for Antwerp for all subjects (Table 5A) and by each subcohort. The PFOA and cholesterol association appeared to primarily reside with the 21 Antwerp employees in subcohort A (Table 5B). This finding can also be observed in Table 2 as the subcohort's mean PFOA levels went from 1.32 ppm. to 2.37 ppm and then declined to 2.06 ppm at the same time their cholesterol values rose from 208 mg/dL to 226 mg/dL to 229 mg/dL. There were no associations between cholesterol and PFOA observed among

the Decatur employee population (Table 5E) nor were there significant associations between TOF and Antwerp or Decatur but when the two sites were combined there was a significant positive association between TOF and cholesterol (Tables 6, 6A and 6B).

There were no significant associations between PFOS, PFOA or TOF with HDL (Tables 7 through 9). BMI, alcoholic drinks per day and cigarettes smoked per day were the most significant associations with HDL.

Triglycerides were not significantly associated with PFOS over time when both Antwerp and Decatur populations were examined together (Table 10). However, among the combined Antwerp and Decatur populations, PFOA was positively associated with triglycerides (Table 11) as seen with the significant positive coefficient for the main effect of PFOA and the nonsignificant positive main coefficient of years and the negative coefficient for their interaction (PFOA x years). The significant main effect of PFOA was the consequence of the Antwerp population (Table 11A) and primarily subcohort A (table 11B) and, to a lesser extent subcohort B (Table 11C), but not subcohort C (Table 11D). Therefore, the association appeared to be related to the Antwerp workers who were enrolled in this longitudinal cohort beginning in 1995, but not 1997. There was not a significant association between PFOA and triglycerides among Decatur workers (Table 11E). Among the Antwerp subcohort A, their mean triglyceride levels rose from 85 mg/dL to 115 mg/dL to 123 mg/dL at the same time their PFOA levels increased from 1.32 ppm to 2.37 ppm and then declined to 2.06 ppm. Although the main effect for TOF was significantly positive, the interaction term with time (years) was not significant (Table 12). Again, this association was more consistent for Antwerp employees (Table 12A) than Decatur employees (Table 12B).

Among the hepatic clinical chemistry tests that were adjusted for the various changing demographic factors and triglyceride levels, there were no significant associations between PFOS, PFOA and TOF with changes in alkaline phosphatase (Tables 13 – 15), GGT (Tables 16-18), AST (Tables 19-21), ALT (Tables 22-24), total bilirubin (Tables 25 – 27) or direct bilirubin (Tables 28-30). Observations apparent in Tables 2 and 3 can also be seen in these mixed model analyses. For example, the two most significant predictors of alkaline phosphatase were time (years) and location (as seen with the lower values among Antwerp employees). For ALT, entry period was also significant as it reflected the higher reference range values for ALT that were used in 1994/95 than in subsequent years.

## DISCUSSION

These analyses were the first longitudinal assessment of the fluorochemical medical surveillance program at 3M's Antwerp and Decatur manufacturing sites. Overall, we observed no associations that were consistent with the toxicological evidence that PFOS produces a hypolipidemic effect at threshold dosages in rats and primates (3M Company 2000; Haughom and Spydevold 1992; Ikeda et al 1987; Pastoor et al 1987; Seacat et al 2001a; 2001b; Sohlenius et al 1993). Our results did suggest a positive association between temporal changes in cholesterol and triglycerides and PFOA; however this is also inconsistent with the toxicological evidence that PFOA may result in a hypolipidemic effect in rats (Haughom and Spydevold 1992; Pastoor et al 1987) but produced no effect on blood lipids in primates (Butenhoff et al 2001).

Even though we were able to perform a longitudinal assessment, there were several limitations to our analyses. We were limited to 175 employees of which only 41 (24 percent) participated in all three surveillance years. Although a greater absolute number of Decatur employees (but not percent-wise) have participated during each year, for this longitudinal assessment there were more Antwerp (57 percent) than Decatur (43 percent) employees. Antwerp employees have had lower serum PFOS level by approximately 0.5 ppm (Olsen et al 1998; Olsen et al 1999a; 1999b; 2001a; 2001b; 2001c). There were insufficient numbers of female employees for any meaningful longitudinal analysis. Given the variability inherent in the analytical method (Hansen et al 2001) and the different laboratories used, serum PFOS and PFOA levels may have systematic error incorporated in each measurement that we were unable to assess as blood samples were analyzed only at the time of the surveillance program. This systematic error may have masked associations with lipid or hepatic clinical chemistries, although the range of PFOS and PFOA measured was relatively consistent throughout the study time period. Because 3M has announced a phase-out of the production of perfluorooctanyl chemistry-related materials, we doubt that there will be many more subjects in the future that can be included in this longitudinal assessment. Also, the findings from this assessment would suggest that serum PFOS levels have either remained constant or declined slightly over time among these 175 employees. On the other hand, serum PFOA levels appeared to trend upwards, on average, by approximately 0.5 to 1.0 ppm for these employees. Another limitation is the fact that the serum PFOS and PFOA levels measured in these employees were lower than those that cause effects in laboratory animals.

In summary, a longitudinal analysis over a six year time period of 175 Antwerp and Decatur male employees did not show significant changes, consistent with toxicological data, of lipid or hepatic clinical chemistry values associated with either PFOS or PFOA. The PFOS and PFOA serum levels measured in these employees were lower than those that cause effects in laboratory animals.

# REFERENCES

3M Company (2000). SIDS Initial assessment report: Perfluorooctane sulfonic acid and its salts. St. Paul (MN):3M Company, (unpublished report).
Minneapolis (MN):University of Minnesota, (unpublished report).

Anderson DJ, Mulvana DE (1997a). Analytical Report for the Determination of Perfluorooctanoate and Perfluorooctanesulfonate in Human Serum by LC/MS. Ithaca NY:Advanced Bioanalytical Services Inc; August 1997.

Anderson DJ, Mulvana DE (1997b). Analytical Report for the Determination of Perfluorooctanoate and Perfluorooctanesulfonate in Human Serum by LC/MS. Ithaca NY:Advanced Bioanalytical Services Inc; September 1997.

Butenhoff JL, Costa G, Elcombe C, Farrar D, Hansen K, Iwai H, Jung R, Kennedy G, Lieder P, Olsen GW, Thomford P. Toxicity of ammonium perfluorooctanoate (APFO) in cynomolgus monkeys after 26 weeks of oral dosing. (unpublished report)

Hansen KJ, Clemen LA, Ellefson ME, Johnson JHO (2001). Compound-specific, quantitative characterization of organic fluorochemicals in biological matrices. Environ Sci Technol 35:766-770.

Haughom B, Spydevold O (1992). The mechanism underlying the hypolipemic effect of perfluoroctanoic acid (PFOA), perfluoroctanesulphonic acid (PFOSA) and clofibric acid. Biochemica et Biophysica Acta 1128:65-72.

Ikeda T, Fukuda K, Mori I, Enomoto M, Komai T, Suga T (1987). Induction of cytochrome P-450 and peroxisome proliferation in rat liver by perfluorinated octanesulfonic acid. In: *Perixosmes in Biology and Medicine*. (HD Fahmi and H Sies, eds) New York:Springer Verlag, pp 304-308.

Johnson JD, Wolter JT, Colaizy GE, Rethwill PA, Nelson RM. Quantification of Perfluorooctanoate and Perfluorooctanesulfonate in Human Serum Using Ion-Pair Extraction and High Performance Liquid Chromatography-Thermospray Mass Spectrometry with Automated Sample Preparation. St. Paul, MN:3M Env Lab, 1996.

Littell RC. Pendergast J, Natarajan R (2000). Modeling covariance structure in the analysis of repeated measures data. Stat Med 19:1793-1819.

Littell RC. Milliken GA, Stroup WW, Wolfinger RD. SAS System for Mixed Models. Cary NC:SAS Institute Inc., 1996, 633 pp.

Olsen GW. Burris JM, Mandel JH, Zobel LR (1998). An epidemiologic investigation of clinical chemistries, hematology and hormones in relation to serum levels of perfluorooctane sulfonate in male fluorochemical production employees. St. Paul:3M Company (unpublished report).

Olsen GW, Burris JM, Mandel JH, Zobel LR (1999a). Serum perfluorooctane sulfonate and hepatic and lipid clinical chemistry tests in fluorochemical production employees. JOEM 41(9):799-806.

Olsen GW, Logan PW, Simpson CA, Hansen KJ, Burris JM, Burlew MM, Schumpert JC, Mandel JH (1999b). Fluorochemical exposure assessment of Decatur chemical and film plant employees. St. Paul:3M Company (unpublished report).

Olsen GW, Burris JM, Burlew MM, Mandel JH (2000). Plasma cholecystokinn and hepatic enzymes, cholesterol and lipoproteins in ammonium perfluorooctanoate production workers. Drug Chem Toxicol 23(4):603-620.

Olsen GW, Burlew MM, Burris JM, Mandel JH (2001a). A cross-sectional analysis of serum perfluorooctansulfonate (PFOS) and perlfuorooctanoate (PFOA) in relation to clinical chemistry, thyroid hormone, hematology and urinalysis results from male and female employee participants of the 2000 Antwerp and Decatur fluorochemical medical surveillance program. St. Paul (MN):3M Company (unpublished report).

Olsen GW, Schmickler MN. Tierens JM, Logan PW, Burris JM, Burlew MM, Lundberg JK, Mandel JH (2001b). Descriptive summary of serum fluorochemical levels among employee participants of the year 2000 Antwerp fluorochemical medical surveillance program. St. Paul:3M Company (unpublished report).

Olsen GW, Logan PW, Simpson CA, Burris JM, Burlew MM, Lundberg JK, Mandel JH (2001c). Descriptive summary of serum fluorochemical levels among employee participants of the year 2000 Decatur fluorochemical medical surveillance program. St Paul:3M Company (unpublished report).

Pastoor TP, Lee KP, Perri MA, Gillies PJ (1987). Biochemical and morphological studies of ammonium perfluorooctanoate-induced hepatomegaly and peroxisome proliferation. Exp Mol Pathol 47:98-109.

Seacat AM, Thomford PJ, Hansen KJ, Clemen LA, Case MT, Butenhoff JL (2001a). Sub-chronic dietary toxicity of potassium perfluorooctanesulfonic acid in rats. Toxicol Sci (submitted 2001a).

Seacat AM, Thoford PJ, Hansen KJ, Olsen GW, Case MT, Butenhoff JL. Subchronic toxicity studies on perfluorooctanesulfonate potassium salt in cynomolgus monkeys. Toxicol Sci (submitted, 2001b).

Sohlenius AK, Eriksson AM, Hogstrom C, Kimland M, DePierre JW (1993). Perfluorooctane sulfonic acid is a potent inducer of peroxisomal fatty acid B-oxidation and other activities known to be affected by peroxisome proliferators in mouse liver. Pharmacol Toxicol 72:90-93.

Table 1. Cross-Sectional Analysis of Mean and Standard Deviation of Serum PFOS, PFOA, TOF, Demographic Characteristics and Clinical Chemistries of Antwerp and Decatur Male Employees Who Participated in Two or More Medical Surveillance Examinations Between 1994/95 and 2000

| | 1994/1995 | | | | 1997 | | | | 2000 | | | |
| | Antwerp (N = 66) | | Decatur (N = 40) | | Antwerp (N = 55) | | Decatur (N = 55) | | Antwerp (N=100) | | Decatur (N = 75) | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PFOS | 1.87 | 1.96 | 2.62[a] | 1.78 | 1.42 | 1.26 | 1.85 | 1.64 | 1.16 | 1.07 | 1.67[b] | 1.39 |
| PFOA | 1.08 | 1.53 | 1.90[b] | 1.08 | 1.54 | 1.61 | 1.41 | 1.17 | 1.43 | 1.21 | 1.83[a] | 1.53 |
| TOF | 1.96 | 1.77 | 3.00[b] | 1.77 | 1.98 | 1.48 | 2.17 | 1.76 | 1.74 | 1.24 | 2.34[b] | 1.72 |
| Age | 36 | 6.6 | 43[d] | 6.0 | 32 | 6.8 | 43[d] | 7.3 | 38 | 7.8 | 47[d] | 7.0 |
| BMI | 23.9 | 2.4 | 28.0[d] | 3.7 | 23.2 | 2.4 | 29.1[d] | 4.3 | 24.7 | 2.8 | 29.0[d] | 4.1 |
| Alcohol | 1.1[d] | 1.1 | 0.3 | 0.6 | 0.9[d] | 1.0 | 0.1 | 0.1 | 1.1[d] | 1.0 | 0.1 | 0.2 |
| Baseline Years Worked | 11.0 | 5.7 | 20.4[d] | 7.1 | 7.0 | 5.2 | 20.0[d] | 6.1 | 9.1 | 6.1 | 20.3[c] | 8.5 |
| Cigarettes | 4 | 7 | 10[b] | 15 | 5 | 7 | 5 | 10 | 5 | 8 | 5 | 11 |
| Cholesterol | 217 | 43 | 219 | 38 | 202 | 45 | 214 | 35 | 220 | 41 | 213 | 40 |
| HDL | 54[d] | 13 | 43 | 13 | 49[c] | 11 | 43 | 10 | 53[d] | 12 | 44 | 10 |
| Triglycerides | 111 | 79 | 204[d] | 122 | 108 | 53 | 181[d] | 112 | 131 | 80 | 178[c] | 115 |
| Alk Phos | 72 | 18 | 103[d] | 27 | 68 | 15 | 87[d] | 20 | 58 | 14 | 74[d] | 21 |
| GGT | 37 | 25 | 47 | 24 | 23 | 11 | 33[a] | 27 | 25 | 19 | 29 | 18 |
| AST | 25 | 11 | 31[a] | 11 | 26 | 6 | 26 | 8 | 24 | 7 | 25 | 7 |
| ALT | 44 | 17 | 49 | 25 | 30 | 12 | 32 | 15 | 23 | 11 | 32[d] | 14 |
| Total Bilirubin | 0.9[d] | 0.4 | 0.5 | 0.2 | 0.8[b] | 0.4 | 0.6 | 0.2 | 1.0[d] | 0.3 | 0.8 | 0.2 |
| Direct Bilirubin | 0.2 | 0.4 | 0.2 | 0.04 | 0.1[b] | 0.07 | 0.1 | 0.04 | 0.1[b] | 0.05 | 0.1 | 0.06 |

Table 2. Cross-Sectional Analysis of Mean and Standard Deviation of Serum PFOS, PFOA, TOF,
Demographic Characteristics and Clinical Chemistries of Three Subgroups of Antwerp Male Employees (A, B and C)
Who Participated in Two or More Medical Surveillance Examinations Between 1995 and 2000

| | 1995 | | | | 1997 | | | | 2000 | | | | | |
| | A (N = 21) | | B (N = 45) | | A (N = 21) | | C (N = 34) | | A (N = 21) | | B (N = 45) | | C (N = 34) | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PFOS | 2.19 | 1.27 | 1.72 | 2.20 | 2.24[a] | 1.32 | 0.91 | 0.93 | 1.53 | 0.87 | 1.20 | 1.31 | 0.87[b] | 0.71 |
| PFOA | 1.32 | 1.28 | 0.96 | 1.64 | 2.37[a] | 2.28 | 1.04 | 0.61 | 2.06[a] | 1.04 | 1.17 | 1.37 | 1.38 | 0.94 |
| TOF | 2.33 | 1.20 | 1.78 | 1.98 | 3.08[a] | 1.59 | 1.31 | 0.91 | 2.41[a] | 0.81 | 1.58 | 1.51 | 1.52 | 0.89 |
| Age | 33 | 6 | 37[a] | 7 | 35[a] | 5 | 30 | 7 | 38[a] | 6 | 42[a] | 7 | 32[a] | 7 |
| BMI | 23.4 | 2.7 | 24.1 | 2.3 | 23.8 | 2.8 | 22.7 | 2.0 | 24.3 | 3.4 | 25.5[c] | 2.7 | 23.9 | 2.4 |
| Drinks/day | 1.3 | 1.4 | 1.0 | 0.9 | 1.2 | 1.2 | 0.7 | 0.8 | 1.7[c] | 1.3 | 1.2 | 1.1 | 0.8 | 0.6 |
| Cigarettes/day | 4 | 7 | 4 | 8 | 5 | 7 | 5 | 7 | 6 | 8 | 4 | 8 | 5 | 8 |
| Baseline Years Worked | 9.9 | 4.3 | 11.6 | 63 | 9.9 | 4.3 | 5.3 | 4.9 | 9.9 | 4.3 | 11.6 | 6.3 | 5.3 | 4.9 |
| Cholesterol | 208 | 46 | 220 | 41 | 226[a] | 50 | 187 | 34 | 229 | 46 | 233[a] | 38 | 196 | 31 |
| HDL | 56 | 11 | 53 | 13 | 51 | 9 | 48 | 11 | 56 | 12 | 52 | 11 | 52 | 13 |
| Triglycerides | 85 | 49 | 123 | 88 | 115 | 69 | 104 | 41 | 123 | 65 | 154 | 95 | 105 | 55 |
| Alk Phos | 69 | 20 | 73 | 16 | 67 | 19 | 69 | 12 | 55 | 17 | 60 | 14 | 58 | 12 |
| GGT | 30 | 9 | 41 | 29 | 25 | 10 | 22 | 11 | 23 | 13 | 30[c] | 25 | 19 | 11 |
| AST | 25 | 5 | 25 | 13 | 26 | 5 | 26 | 7 | 22 | 5 | 25 | 9 | 23 | 6 |
| ALT | 42 | 8 | 46 | 20 | 31 | 12 | 30 | 13 | 22 | 11 | 25 | 13 | 21 | 7 |
| Total Bilirubin | 1.0 | 0.3 | 0.8 | 0.4 | 0.8 | 0.3 | 0.8 | 0.4 | 1.0 | 0.3 | 1.0 | 0.3 | 0.9 | 0.3 |
| Direct Bilirubin | 0.2 | 0.04 | 0.2 | 0.04 | 0.1 | 0.05 | 0.2 | 0.08 | 0.1 | 0.03 | 0.1 | 0.06 | 0.1 | 0.06 |

Table 3. Cross-Sectional Analysis of Mean and Standard Deviation of Serum PFOS, PFOA, TOF, Demographic Characteristics and Clinical Chemistries of Three Subgroups of Decatur Male Employees (A, B and C) Who Participated in Two or More Medical Surveillance Examinations Between 1994 and 2000

| | 1994 | | | | 1997 | | | | 2000 | | | | | |
| | A (N = 20) | | B (N = 20) | | A (N = 20) | | C (N = 35) | | A (N = 20) | | B (N = 20) | | C (N = 35) | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PFOS | 2.07 | 1.67 | 3.17[a] | 1.76 | 1.93 | 1.76 | 1.80 | 1.59 | 1.78 | 2.14 | 1.84 | 1.03 | 1.51 | 0.98 |
| PFOA | 1.50 | 0.87 | 2.30[a] | 1.14 | 1.41 | 1.16 | 1.41 | 1.20 | 1.46 | 1.34 | 2.60[a] | 2.02 | 1.60 | 1.14 |
| TOF | 2.37 | 1.54 | 3.64[a] | 1.79 | 2.22 | 1.78 | 2.14 | 1.78 | 2.16 | 2.16 | 2.98 | 1.76 | 2.08 | 1.32 |
| Age | 42 | 7 | 44 | 5 | 45 | 7 | 42 | 8 | 48 | 7 | 50 | 5 | 45 | 8 |
| BMI | 28.2 | 4.0 | 27.7 | 3.3 | 28.3 | 4.1 | 29.6 | 4.5 | 28.9 | 4.1 | 28.7 | 3.3 | 29.3 | 4.5 |
| Drinks/day | 0.1 | 0.3 | 0.4 | 0.8 | 0.1 | 0.1 | 0.1 | 0.2 | 0.0 | 0.1 | 0.2 | 0.3 | 0.1 | 0.2 |
| Cigarettes/day | 6 | 13 | 14 | 15 | 4 | 10 | 5 | 11 | 3 | 8 | 10 | 15 | 4 | 9 |
| Baseline Years Worked | 19.6 | 8.6 | 21.3 | 5.2 | 19.6 | 8.6 | 20.2 | 10.0 | 19.6 | 8.6 | 21.3 | 5.2 | 20.2 | 10.0 |
| Cholesterol | 235[a] | 34 | 204 | 36 | 223 | 31 | 208 | 37 | 228 | 39 | 199[b] | 33 | 212 | 41 |
| HDL | 47[a] | 16 | 39 | 9 | 45 | 11 | 41 | 9 | 47 | 12 | 38[a] | 6 | 45 | 9 |
| Triglycerides | 180 | 88 | 229 | 148 | 188 | 115 | 178 | 112 | 193 | 124 | 187 | 76 | 165 | 128 |
| Alk Phos | 98 | 29 | 107 | 24 | 85 | 22 | 87 | 18 | 70 | 27 | 82 | 17 | 72 | 20 |
| GGT | 41 | 25 | 52 | 22 | 35 | 36 | 31 | 20 | 29 | 16 | 34 | 23 | 27 | 17 |
| AST | 32 | 15 | 29 | 6 | 25 | 6 | 27 | 8 | 26 | 8 | 25 | 4 | 25 | 7 |
| ALT | 52 | 33 | 47 | 11 | 30 | 15 | 34 | 16 | 30 | 18 | 32 | 11 | 33 | 14 |
| Total Bilirubin | 0.6 | 0.2 | 0.5 | 0.2 | 0.6 | 0.2 | 0.6 | 0.2 | 0.8 | 0.2 | 0.7 | 0.2[c] | 0.8 | 0.2 |
| Direct Bilirubin | 0.2[a] | 0.05 | 0.2 | 0.04 | 0.1 | 0.04 | 0.1 | 0.05 | 0.1 | 0.08 | 0.1 | 0.04 | 0.1 | 0.1 |

Table 4. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of Cholesterol[#] Change Including PFOS and the Interaction with
Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 4.868 | 0.127 | <.0001 | 4.618 | 5.118 |
| PFOS | 0.010 | 0.008 | .18 | -0.005 | 0.025 |
| Years Observation | 0.0009 | 0.005 | .84 | -0.008 | 0.010 |
| PFOS x Years Obs | -0.0004 | 0.002 | .83 | -0.004 | 0.003 |
| Age | 0.007 | 0.003 | .01 | 0.002 | 0.013 |
| BMI | 0.006 | 0.003 | .07 | -0.0005 | 0.013 |
| Drinks/day | 0.014 | 0.012 | .27 | -0.011 | 0.038 |
| Cigarettes/day | -0.0009 | 0.001 | .41 | -0.003 | 0.001 |
| Location* | 0.034 | 0.037 | .36 | -0.039 | 0.108 |
| Entry Period** | 0.064 | 0.028 | .02 | 0.009 | 0.119 |
| Baseline Years Worked | -0.004 | 0.003 | .20 | -0.009 | 0.002 |

[#]natural log
*Antwerp vs Decatur
**1994/95 vs 1997

Table 5. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of Cholesterol[#] Change Including PFOA and the Interaction with
Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| Intercept | 4.812 | 0.127 | <.0001 | 4.561 | 5.063 |
| PFOA | 0.032 | 0.009 | .0008 | 0.013 | 0.051 |
| Years Observation | 0.005 | 0.005 | .24 | -0.004 | 0.014 |
| PFOA x Years Obs | -0.005 | 0.002 | .005 | -0.009 | -0.002 |
| Age | 0.008 | 0.003 | .007 | 0.002 | 0.013 |
| BMI | 0.007 | 0.003 | .049 | 0.00004 | 0.013 |
| Drinks/day | 0.014 | 0.012 | .263 | -0.010 | 0.037 |
| Cigarettes/day | -0.001 | 0.001 | .32 | -0.003 | 0.001 |
| Location* | 0.041 | 0.037 | .27 | -0.032 | 0.114 |
| Entry Period** | 0.068 | 0.027 | .01 | 0.015 | 0.122 |
| Baseline Years Worked | -0.004 | 0.003 | .15 | -0.009 | 0.001 |

#natural log
*Antwerp vs Decatur
**1994/95 vs 1997

Table 5A. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of Cholesterol[#] Change Including PFOA and the Interaction with Number of Years of Observation of Antwerp Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 4.710 | 0.149 | <.0001 | 4.414 | 5.005 |
| PFOA | 0.029 | 0.012 | .01 | 0.006 | 0.053 |
| Years Observation | 0.005 | 0.006 | .36 | -0.006 | 0.017 |
| PFOA x Years Obs | -0.003 | 0.003 | .20 | -0.009 | 0.002 |
| Age | 0.009 | 0.003 | .008 | 0.003 | 0.016 |
| BMI | 0.008 | 0.005 | .14 | -0.003 | 0.019 |
| Drinks/day | 0.022 | 0.013 | .09 | -0.004 | 0.047 |
| Cigarettes/day | 0.0007 | 0.002 | .70 | -0.003 | 0.004 |
| Entry Period** | 0.079 | 0.038 | .04 | 0.004 | 0.153 |
| Baseline Years Worked | -0.002 | 0.004 | .67 | -0.010 | 0.007 |

#natural log
**1994/95 vs 1997

000278

Table 5B. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of Cholesterol[#] Change Including PFOA and the Interaction with Number of Years of Observation of Antwerp Subgroup A (1995, 1997 and 2000) Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 5.059 | 0.414 | <.0001 | 4.194 | 5.925 |
| PFOA | 0.044 | 0.020 | .03 | 0.004 | 0.084 |
| Years Observation | 0.037 | 0.015 | .02 | 0.007 | 0.067 |
| PFOA x Years Obs | -0.013 | 0.005 | .02 | -0.023 | -0.002 |
| Age | -0.0007 | 0.012 | .95 | -0.025 | 0.024 |
| BMI | 0.004 | 0.012 | .77 | -0.020 | 0.028 |
| Drinks/day | -0.016 | 0.019 | .41 | -0.054 | 0.023 |
| Cigarettes/day | 0.003 | 0.005 | .51 | -0.007 | 0.013 |
| Baseline Years Worked | 0.015 | 0.016 | .36 | -0.018 | 0.047 |

[#]natural log

Table 5C. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of Cholesterol[#] Change Including PFOA and the Interaction with Number of Years of Observation of Antwerp Subgroup B (1995 and 2000) Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 4.838 | 0.244 | <0.001 | 4.346 | 5.330 |
| PFOA | 0.018 | 0.017 | .30 | -0.016 | 0.052 |
| Years Observation | 0.005 | 0.008 | .55 | -0.011 | 0.021 |
| PFOA x Years Obs | -0.002 | 0.004 | .58 | -0.009 | 0.005 |
| Age | 0.004 | 0.005 | .40 | -0.006 | 0.015 |
| BMI | 0.014 | 0.009 | .13 | -0.004 | 0.031 |
| Drinks/day | 0.017 | 0.022 | .45 | -0.028 | 0.061 |
| Cigarettes/day | 0.002 | 0.003 | .44 | -0.004 | 0.009 |
| Baseline Years Worked | -0.0001 | 0.006 | .99 | -0.011 | 0.011 |

[#]natural log

000280

Table 5D. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of Cholesterol[#] Change Including PFOA and the Interaction with Number of Years of Observation of Antwerp Subgroup C (1997 and 2000) Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 4.528 | 0.281 | <.0001 | 3.955 | 5.100 |
| PFOA | 0.004 | 0.062 | .95 | -0.125 | 0.132 |
| Years Observation | -0.010 | 0.026 | .70 | -0.065 | 0.044 |
| PFOA x Years Obs | 0.010 | 0.022 | .65 | -0.035 | 0.055 |
| Age | 0.016 | 0.006 | .01 | 0.004 | 0.028 |
| BMI | 0.009 | 0.012 | .43 | -0.015 | 0.033 |
| Drinks/day | 0.033 | 0.032 | .31 | -0.033 | 0.100 |
| Cigarettes/day | -0.0001 | 0.003 | .97 | -0.007 | 0.006 |
| Baseline Years Work | -0.005 | 0.008 | .49 | -0.021 | 0.011 |

[#]natural log

Table 5F. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of Cholesterol# Change Including PFOA and the Interaction with
Number of Years of Observation of Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 5.220 | 0.206 | <.0001 | 4.810 | 5.630 |
| PFOA | 0.016 | 0.016 | .34 | -0.017 | 0.048 |
| Years Observation | -0.002 | 0.008 | .77 | -0.017 | 0.013 |
| PFOA x Years Obs | -0.003 | 0.003 | .22 | -0.009 | 0.002 |
| Age | 0.002 | 0.005 | .70 | -0.008 | 0.012 |
| BMI | 0.003 | 0.004 | .55 | -0.006 | 0.011 |
| Drinks/day | -0.088 | 0.035 | .01 | -0.158 | -0.018 |
| Cigarettes/day | -0.002 | 0.001 | .15 | -0.004 | 0.0007 |
| Entry Period** | 0.047 | 0.040 | .24 | -0.032 | 0.125 |
| Baseline Years Worked | -0.002 | 0.004 | .62 | -0.010 | 0.006 |

#natural log
**1994/95 vs 1997

000282

Table 6. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of Cholesterol[*] Change Including TOF and the Interaction with Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| | | | | Lower | Upper |
|---|---|---|---|---|---|
| Intercept | 4.828 | 0.127 | <.0001 | 4.577 | 5.079 |
| TOF | 0.021 | 0.008 | .007 | 0.006 | 0.035 |
| Years Observation | 0.004 | 0.005 | .37 | -0.005 | 0.014 |
| TOF x Years Obs | -0.003 | 0.001 | .07 | -0.005 | 0.0003 |
| Age | 0.007 | 0.003 | .01 | 0.002 | 0.013 |
| BMI | 0.006 | 0.003 | .05 | -0.0001 | 0.013 |
| Drinks/day | 0.012 | 0.012 | .32 | -0.012 | 0.036 |
| Cigarettes/day | -0.001 | 0.001 | .37 | -0.003 | 0.001 |
| Location* | 0.042 | 0.037 | .26 | -0.032 | 0.115 |
| Entry Period** | 0.063 | 0.027 | .02 | 0.010 | 0.117 |
| Baseline Years Worked | -0.004 | 0.003 | .17 | -0.009 | 0.002 |

#natural log
*Antwerp vs Decatur
**1994/95 vs 1997

Table 6A. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of Cholesterol[#] Change Including TOF and the Interaction with Number of Years of Observation of Antwerp Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 4.721 | 0.150 | < .0001 | 4.424 | 5.018 |
| TOF | 0.017 | 0.011 | .12 | - 0.004 | 0.038 |
| Years Observation | 0.004 | 0.007 | .55 | - 0.009 | 0.017 |
| TOF x Years Obs | - 0.0008 | 0.002 | .70 | - 0.005 | 0.003 |
| Age | 0.009 | 0.003 | .01 | 0.002 | 0.016 |
| BMI | 0.009 | 0.006 | .12 | - 0.002 | 0.020 |
| Drinks/day | 0.019 | 0.013 | .14 | - 0.006 | 0.045 |
| Cigarettes/day | 0.0008 | 0.002 | .69 | - 0.003 | 0.005 |
| Entry Period** | 0.070 | 0.038 | .07 | - 0.006 | 0.145 |
| Baseline Years Worked | - 0.0008 | 0.004 | .85 | - 0.009 | 0.008 |

[#]natural log
**1994/95 vs 1997

Table 6B. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of Cholesterol[#] Change Including TOF and the Interaction with
Number of Years of Observation of Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 5.214 | 0.202 | <.0001 | 4.811 | 5.616 |
| TOF | 0.014 | 0.011 | .19 | -0.007 | 0.035 |
| Years Observation | -0.002 | 0.008 | .79 | -0.018 | 0.013 |
| TOF x Years Obs | -0.002 | 0.002 | .22 | -0.006 | 0.001 |
| Age | 0.002 | 0.005 | .69 | -0.008 | 0.012 |
| BMI | 0.002 | 0.004 | .55 | -0.006 | 0.011 |
| Drinks/day | -0.090 | 0.035 | .012 | -0.160 | -0.020 |
| Cigarettes/day | -0.002 | 0.001 | .161 | -0.004 | 0.0007 |
| Baseline Years Worked | -0.002 | 0.004 | .60 | -0.010 | 0.006 |

[#] natural log
[**] 1994/95 vs 1997

Table 7. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of HDL# Change Including PFOS and the Interaction with
Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| | | | | Lower | Upper |
| --- | --- | --- | --- | --- | --- |
| Intercept | 4.212 | 0.144 | <.0001 | 3.930 | 4.495 |
| PFOS | - 0.010 | 0.008 | .24 | - 0.026 | 0.007 |
| Years Observation | 0.002 | 0.005 | .71 | - 0.008 | 0.012 |
| PFOS x Years Obs | - 0.001 | 0.002 | .52 | - 0.005 | 0.002 |
| Age | 0.004 | 0.003 | .22 | - 0.002 | 0.011 |
| BMI | - 0.017 | 0.004 | <.0001 | - 0.025 | 0.010 |
| Drinks/day | 0.064 | 0.013 | <.0001 | 0.037 | 0.090 |
| Cigarettes/day | - 0.004 | 0.001 | .0005 | - 0.007 | - 0.002 |
| Location* | 0.006 | 0.043 | .89 | - 0.079 | 0.091 |
| Entry Period** | 0.025 | 0.032 | .44 | - 0.038 | 0.088 |
| Baseline Years Worked | - 0.007 | 0.003 | .03 | - 0.013 | - 0.0005 |

#natural log
*Antwerp vs Decatur
**1994/95 vs 1997

Table 8. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of HDL# Change Including PFOA and the Interaction with
Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| | | | | Lower | Upper |
|---|---|---|---|---|---|
| Intercept | 4.216 | 0.145 | <.0001 | 3.929 | 4.503 |
| PFOA | -0.006 | 0.011 | .56 | -0.027 | 0.015 |
| Years Observation | 0.005 | 0.005 | .35 | -0.005 | 0.014 |
| PFOA x Years Obs | -0.002 | 0.002 | .40 | -0.006 | 0.002 |
| Age | 0.004 | 0.003 | .28 | -0.003 | 0.010 |
| BMI | -0.017 | 0.004 | <.0001 | -0.024 | -0.010 |
| Drinks/day | 0.062 | 0.013 | <.0001 | 0.036 | 0.088 |
| Cigarettes/day | -0.004 | 0.001 | .0004 | -0.007 | -0.002 |
| Location* | 0.008 | 0.043 | .85 | -0.076 | 0.093 |
| Entry Period** | 0.020 | 0.032 | .53 | -0.042 | 0.082 |
| Baseline Years Worked | -0.007 | 0.003 | .04 | -0.013 | -0.0004 |

#natural log
*Antwerp vs Decatur
**1994/95 vs 1997

Table 9. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of HDL\* Change Including TOF and the Interaction with Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 4.217 | 0.145 | <.0001 | 3.931 | 4.502 |
| TOF | - 0.006 | 0.008 | .44 | - 0.023 | 0.010 |
| Years Observation | 0.004 | 0.005 | .47 | - 0.007 | 0.014 |
| TOF x Years Obs | - 0.0009 | 0.001 | .57 | - 0.004 | 0.002 |
| Age | 0.004 | 0.003 | .25 | - 0.003 | 0.010 |
| BMI | - 0.017 | 0.004 | <.0001 | - 0.025 | - 0.010 |
| Drinks/day | 0.063 | 0.013 | <.0001 | 0.037 | 0.089 |
| Cigarettes/day | - 0.004 | 0.001 | .0005 | - 0.007 | - 0.002 |
| Location* | 0.007 | 0.043 | .88 | - 0.078 | 0.092 |
| Entry Period** | 0.021 | 0.032 | .50 | - 0.041 | 0.084 |
| Baseline Years Worked | - 0.007 | 0.003 | .04 | - 0.013 | - 0.0004 |

\*natural log
\*Antwerp vs Decatur
\*\*1994/95 vs 1997

Table 10. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of Triglyceride[#] Change Including PFOS and the Interaction with Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 2.730 | 0.335 | <.0001 | 2.068 | 3.392 |
| PFOS | 0.025 | 0.020 | .22 | -0.015 | 0.065 |
| Years Observation | -0.004 | 0.013 | .73 | -0.029 | 0.021 |
| PFOS x Years Obs | 0.006 | 0.005 | .22 | -0.004 | 0.015 |
| Age | 0.003 | 0.008 | .67 | -0.011 | 0.018 |
| BMI | 0.006 | 0.009 | <.0001 | 0.048 | 0.083 |
| Drinks/day | -0.029 | 0.033 | .37 | -0.094 | 0.035 |
| Cigarettes/day | 0.011 | 0.003 | .0002 | 0.005 | 0.017 |
| Location* | 0.052 | 0.099 | .60 | -0.143 | 0.247 |
| Entry Period** | 0.089 | 0.073 | .22 | -0.055 | 0.234 |
| Baseline Years Worked | 0.005 | 0.007 | .50 | -0.010 | 0.019 |

[#]natural log
* Antwerp vs Decatur
**1994/95 vs 1997

Table 11. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of Triglyceride# Change Including PFOA and the Interaction with
Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| | | | | Lower | Upper |
| --- | --- | --- | --- | --- | --- |
| Intercept | 2.539 | 0.332 | <.0001 | 1.883 | 3.196 |
| PFOA | 0.094 | 0.025 | .0002 | 0.045 | 0.144 |
| Years Observation | 0.007 | 0.012 | .57 | -0.017 | 0.031 |
| PFOA x Years Obs | -0.008 | 0.005 | .12 | -0.018 | 0.002 |
| Age | 0.006 | 0.007 | .42 | -0.009 | 0.021 |
| BMI | 0.066 | 0.009 | <.0001 | 0.049 | 0.083 |
| Drinks/day | -0.027 | 0.032 | .40 | -0.090 | 0.037 |
| Cigarettes/day | 0.011 | 0.003 | .0002 | 0.005 | 0.017 |
| Location* | 0.072 | 0.096 | .46 | -0.118 | 0.262 |
| Entry Period** | 0.098 | 0.070 | .17 | -0.041 | 0.236 |
| Baseline Years Worked | 0.003 | 0.007 | .67 | -0.011 | 0.017 |

#natural log
*Antwerp vs Decatur
**1994/95 vs 1997

000290

Table 11A. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of Triglyceride* Change Including PFOA and the Interaction with Number of Years of Observation of Antwerp Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 3.067 | 0.394 | <.0001 | 2.286 | 3.848 |
| PFOA | 0.089 | 0.030 | .005 | 0.028 | 0.149 |
| Years Observation | 0.024 | 0.015 | .12 | -0.006 | 0.053 |
| PFOA x Years Obs | -0.010 | 0.007 | .15 | -0.023 | 0.004 |
| Age | 0.012 | 0.009 | .22 | -0.007 | 0.030 |
| BMI | 0.039 | 0.014 | .007 | 0.011 | 0.068 |
| Drinks/day | -0.026 | 0.033 | .44 | -0.092 | 0.040 |
| Cigarettes/day | 0.018 | 0.005 | .0004 | 0.008 | 0.028 |
| Entry Period** | 0.013 | 0.100 | .90 | -0.212 | 0.186 |
| Baseline Years Worked | 0.003 | 0.011 | .76 | -0.019 | 0.026 |

*natural log
**1994/95 vs 1997

000291

Table 11B. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of Triglyceride[#] Change Including PFOA and the Interaction with Number of Years of Observation of Antwerp Subgroup A (1995, 1997 and 2000) Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 3.104 | 1.063 | .009 | 0.880 | 5.328 |
| PFOA | 0.182 | 0.051 | .001 | 0.079 | 0.286 |
| Years Observation | 0.167 | 0.037 | < .0001 | 0.091 | 0.241 |
| PFOA x Years Obs | - 0.061 | 0.011 | < .0001 | - 0.084 | - 0.039 |
| Age | - 0.007 | 0.031 | .83 | - 0.069 | 0.056 |
| BMI | 0.039 | 0.030 | .20 | - 0.021 | 0.100 |
| Drinks/day | - 0.082 | 0.051 | .12 | - 0.186 | 0.023 |
| Cigarettes/day | 0.008 | 0.012 | .52 | - 0.017 | 0.033 |
| Baseline Years Worked | 0.036 | 0.041 | .40 | - 0.049 | 0.120 |

[#]natural log

Table 11C. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of Triglyceride[#] Change Including PFOA and the Interaction with
Number of Years of Observation of Antwerp Subgroup B (1995 and 2000) Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 2.775 | 0.523 | <.0001 | 1.720 | 3.830 |
| PFOA | 0.097 | 0.038 | .02 | 0.019 | 0.174 |
| Years Observation | 0.005 | 0.018 | .80 | -0.033 | 0.042 |
| PFOA x Years Obs | 0.0008 | 0.009 | .93 | -0.017 | 0.018 |
| Age | 0.019 | 0.011 | .10 | -0.004 | 0.041 |
| BMI | 0.042 | 0.019 | .04 | 0.003 | 0.081 |
| Drinks/day | 0.038 | 0.050 | .45 | -0.062 | 0.138 |
| Cigarettes/day | 0.022 | 0.007 | .003 | 0.008 | 0.036 |
| Baseline Years Worked | -0.002 | 0.012 | .83 | -0.026 | 0.021 |

[#]natural log

Table 11D. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of Triglyceride[#] Change Including PFOA and the Interaction with Number of Years of Observation of Antwerp Subgroup C (1997 and 2000) Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 3.285 | 0.744 | .0001 | 1.769 | 4.801 |
| PFOA | 0.032 | 0.149 | .83 | -0.280 | 0.344 |
| Years Observation | -0.072 | 0.063 | .26 | -0.203 | 0.058 |
| PFOA x Years Obs | 0.020 | 0.051 | .70 | -0.087 | 0.128 |
| Age | -0.005 | 0.016 | .77 | -0.038 | 0.028 |
| BMI | 0.057 | 0.030 | .08 | -0.006 | 0.120 |
| Drinks/day | -0.025 | 0.081 | .76 | 0.195 | 0.145 |
| Cigarettes/day | 0.019 | 0.008 | .032 | 0.002 | 0.036 |
| Baseline Years Worked | 0.010 | 0.021 | .65 | -0.034 | 0.053 |

[#]natural log

000294

Table 11E: Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of Triglyceride[#] Change Including PFOA and the Interaction with
Number of Years of Observation of Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 2.581 | 0.567 | <.0001 | 1.450 | 3.712 |
| PFOA | 0.054 | 0.046 | .24 | -0.037 | 0.145 |
| Years Observation | -0.028 | 0.022 | .20 | -0.071 | 0.015 |
| PFOA x Years Obs | 0.002 | 0.008 | .85 | -0.014 | 0.017 |
| Age | -0.0008 | 0.013 | .95 | -0.028 | 0.026 |
| BMI | 0.073 | 0.012 | <.0001 | 0.050 | 0.096 |
| Drinks/day | -0.038 | 0.099 | .70 | -0.235 | 0.158 |
| Cigarettes/day | 0.005 | 0.004 | .16 | -0.002 | 0.012 |
| Entry Period** | 0.274 | 0.109 | .01 | 0.058 | 0.491 |
| Baseline Years Worked | 0.009 | 0.011 | .44 | -0.013 | 0.030 |

[#]natural log
**1994/95 vs 1997

Table 12. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of Triglyceride# Change Including TOF and the Interaction with
Number of Years of Observation of Antwerp and Decatur Male Employees

|  | Coefficient | SE | p-value | 95% Confidence Limits | |
|---|---|---|---|---|---|
|  |  |  |  | Lower | Upper |
| Intercept | 2.612 | 0.334 | <.0001 | 1.953 | 3.272 |
| TOF | 0.053 | 0.020 | .008 | 0.014 | 0.093 |
| Years Observation | -0.0005 | 0.013 | .97 | -0.027 | 0.026 |
| TOF x Years Obs | -0.0005 | 0.004 | .91 | -0.008 | 0.007 |
| Age | 0.004 | 0.007 | .57 | -0.010 | 0.019 |
| BMI | 0.066 | 0.009 | <.0001 | 0.049 | 0.084 |
| Drinks/day | -0.031 | 0.032 | .34 | -0.095 | 0.033 |
| Cigarettes/day | 0.011 | 0.003 | .0002 | 0.005 | 0.017 |
| Location* | 0.074 | 0.098 | .45 | -0.119 | 0.266 |
| Entry Period** | 0.085 | 0.071 | .23 | -0.055 | 0.226 |
| Baseline Years Worked | 0.004 | 0.007 | .58 | -0.010 | 0.018 |

#natural log
* Antwerp vs Decatur
**1994/95 vs 1997

Table 12A. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of Triglyceride[#] Change Including TOF and the Interaction with Number of Years of Observation for Antwerp Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 3.078 | 0.395 | < .0001 | 2.294 | 3.862 |
| TOF | 0.053 | 0.028 | .06 | - 0.002 | 0.107 |
| Years Observation | 0.016 | 0.017 | .35 | - 0.018 | 0.049 |
| TOF x Years Obs | - 0.0007 | 0.006 | .90 | - 0.012 | 0.010 |
| Age | 0.009 | 0.009 | .32 | - 0.009 | 0.028 |
| BMI | 0.042 | 0.014 | 0.004 | 0.014 | 0.071 |
| Drinks/day | - 0.032 | 0.034 | .34 | - 0.099 | 0.035 |
| Cigarettes/day | 0.018 | 0.005 | .0005 | 0.008 | 0.029 |
| Entry Period** | - 0.045 | 0.101 | .66 | - 0.245 | 0.155 |
| Baseline Years Worked | 0.007 | 0.011 | .56 | - 0.016 | 0.029 |

#natural log
**1994/95 vs 1997

Table 12B. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of Triglyceride[*] Change Including TOF and the Interaction with Number of Years of Observation for Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 2.644 | 0.563 | <.0001 | 1.521 | 3.766 |
| TOF | 0.031 | 0.030 | .29 | -0.028 | 0.090 |
| Years Observation | -0.035 | 0.022 | .12 | -0.079 | 0.009 |
| TOF x Years Obs | 0.004 | 0.005 | .45 | -0.007 | 0.015 |
| Age | -0.002 | 0.014 | .90 | -0.029 | 0.025 |
| BMI | 0.073 | 0.012 | <.0001 | 0.050 | 0.010 |
| Drinks/day | -0.030 | 0.099 | .76 | -0.227 | 0.166 |
| Cigarettes/day | 0.005 | 0.004 | .20 | -0.003 | 0.012 |
| Entry Period** | 0.275 | 0.111 | .01 | 0.055 | 0.494 |
| Baseline Years Worked | 0.009 | 0.011 | .44 | -0.013 | 0.030 |

*natural log
**1994/95 vs 1997

Table 13. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of Alkaline Phosphatase[#] Change Including PFOS and the Interaction with
Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 3.789 | 0.176 | < .0001 | 3.442 | 4.137 |
| PFOS | 0.002 | 0.009 | .87 | -0.017 | 0.020 |
| Years Observation | -0.051 | 0.006 | < .0001 | -0.062 | -0.040 |
| PFOS x Years Obs | 0.002 | 0.002 | .47 | -0.003 | 0.006 |
| Age | 0.005 | 0.004 | .20 | -0.003 | 0.012 |
| BMI | -0.0007 | 0.004 | .88 | -0.009 | 0.008 |
| Drinks/day | -0.001 | 0.014 | .94 | -0.030 | 0.028 |
| Cigarettes/day | 0.003 | 0.001 | .03 | 0.0004 | 0.006 |
| Location* | -0.242 | 0.049 | < .0001 | -0.338 | -0.145 |
| Entry Period** | 0.098 | 0.037 | .008 | 0.025 | 0.171 |
| Baseline Years Worked | -0.006 | 0.004 | .10 | -0.013 | 0.001 |
| Triglycerides[#] | 0.113 | 0.024 | < .0001 | 0.067 | 0.160 |

[#]natural log
* Antwerp vs Decatur
** 1994/95 vs 1997

Table 14. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of Alkaline Phosphatase# Change Including PFOA and the Interaction with
Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 3.785 | 0.176 | <.0001 | 3.437 | 4.133 |
| PFOA | 0.005 | 0.012 | .69 | -0.019 | 0.028 |
| Years Observation | -0.047 | 0.006 | <.0001 | -0.058 | -0.036 |
| PFOA x Years Obs | -0.001 | 0.002 | .62 | -0.005 | 0.003 |
| Age | 0.005 | 0.004 | .19 | -0.002 | 0.013 |
| BMI | -0.0009 | 0.004 | .85 | -0.010 | 0.008 |
| Drinks/day | -0.002 | 0.015 | .89 | -0.031 | 0.027 |
| Cigarettes/day | 0.003 | 0.001 | .03 | 0.0004 | 0.006 |
| Location* | -0.243 | 0.049 | <.0001 | -0.340 | -0.147 |
| Entry Period** | 0.100 | 0.036 | .007 | 0.028 | 0.172 |
| Baseline Years Worked | -0.006 | 0.004 | .09 | -0.014 | 0.001 |
| Triglycerides# | 0.114 | 0.024 | <.0001 | 0.066 | 0.161 |

#natural log
*Antwerp vs Decatur
**1994/95 vs 1997

Table 15. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of Alkaline Phosphatase[#] Change Including TOF and the Interaction with Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits Lower | 95% Confidence Limits Upper |
|---|---|---|---|---|---|
| Intercept | 3.789 | 0.177 | <.0001 | 3.441 | 4.138 |
| TOF | -0.00004 | 0.009 | .99 | -0.019 | 0.018 |
| Years Observation | -0.049 | 0.006 | <.0001 | -0.060 | -0.037 |
| TOF x Years Obs | -0.00006 | 0.0017 | .97 | -0.003 | 0.003 |
| Age | 0.005 | 0.004 | .19 | -0.003 | 0.012 |
| BMI | -0.001 | 0.004 | .82 | -0.010 | 0.008 |
| Drinks/day | -0.002 | 0.015 | .91 | -0.031 | 0.028 |
| Cigarettes/day | 0.003 | 0.001 | .03 | 0.0004 | 0.006 |
| Location* | -0.245 | 0.049 | <.0001 | -0.342 | -0.148 |
| Entry Period** | 0.100 | 0.036 | .007 | 0.028 | 0.172 |
| Baseline Years Worked | -0.006 | 0.004 | .10 | -0.013 | 0.001 |
| Triglycerides[#] | 0.115 | 0.024 | <.0001 | 0.068 | 0.162 |

[#]natural log
*Antwerp vs Decatur
**1994/95 vs 1997

Table 16. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of GGT$^{\#}$ Change Including PFOS and the Interaction with
Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 1.883 | 0.373 | <.0001 | 1.146 | 2.620 |
| PFOS | -0.004 | 0.020 | .84 | -0.043 | 0.035 |
| Years Observation | -0.075 | 0.012 | <.0001 | -0.098 | -0.051 |
| PFOS x Years Obs | 0.004 | 0.004 | .42 | -0.005 | 0.012 |
| Age | -0.003 | 0.008 | .74 | -0.019 | 0.013 |
| BMI | 0.005 | 0.009 | .59 | -0.013 | 0.024 |
| Drinks/day | 0.042 | 0.031 | .18 | -0.020 | 0.104 |
| Cigarettes/day | -0.0009 | 0.003 | .77 | -0.007 | 0.005 |
| Location* | -0.096 | 0.104 | .36 | -0.030 | 0.110 |
| Entry Period** | 0.358 | 0.078 | <.0001 | 0.204 | 0.512 |
| Baseline Years Worked | 0.008 | 0.007 | .30 | -0.007 | 0.024 |
| Triglycerides$^{\#}$ | 0.251 | 0.050 | <.0001 | 0.152 | 0.350 |

$^{\#}$natural log
*Antwerp vs Decatur
**1994/95 vs 1997

Table 17. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of GGT[#] Change Including PFOA and the Interaction with Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 1.876 | 0.374 | <.0001 | 1.138 | 2.613 |
| PFOA | -0.009 | 0.025 | .72 | -0.058 | 0.040 |
| Years Observation | -0.077 | 0.012 | <.0001 | -0.100 | -0.054 |
| PFOA x Years Obs | 0.005 | 0.005 | .29 | -0.004 | 0.014 |
| Age | -0.002 | 0.008 | .76 | -0.018 | 0.013 |
| BMI | 0.004 | 0.009 | .64 | -0.014 | 0.023 |
| Drinks/day | 0.043 | 0.031 | .17 | -0.019 | 0.105 |
| Cigarettes/day | -0.0007 | 0.003 | .82 | -0.007 | 0.005 |
| Location* | -0.097 | 0.104 | .35 | -0.301 | 0.108 |
| Entry Period** | 0.355 | 0.077 | <.0001 | 0.203 | 0.507 |
| Baseline Years Worked | 0.008 | 0.008 | .30 | -0.007 | 0.024 |
| Triglycerides[#] | 0.256 | 0.051 | <.0001 | 0.156 | 0.356 |

[#]natural log
*Antwerp vs Decatur
**1994/95 vs 1997

Table 18. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of GGT$^{\#}$ Change Including TOF and the Interaction with
Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 1.870 | 0.374 | < .0001 | 1.132 | 2.608 |
| TOF | 0.002 | 0.020 | .93 | - 0.037 | 0.041 |
| Years Observation | - 0.079 | 0.013 | < .0001 | - 0.104 | - 0.054 |
| TOF x Years Obs | 0.004 | 0.003 | .25 | - 0.003 | 0.011 |
| Age | - 0.003 | 0.008 | .75 | - 0.018 | 0.013 |
| BMI | 0.005 | 0.009 | .57 | - 0.013 | 0.024 |
| Drinks/day | 0.043 | 0.031 | .17 | - 0.019 | 0.104 |
| Cigarettes/day | - 0.0009 | 0.003 | .77 | - 0.007 | 0.005 |
| Location* | - 0.088 | 0.104 | .40 | - 0.294 | 0.117 |
| Entry Period** | 0.352 | 0.078 | < .0001 | 0.200 | 0.505 |
| Baseline Years Worked | 0.008 | 0.008 | .31 | - 0.007 | 0.024 |
| Triglycerides$^{\#}$ | 0.249 | 0.050 | < .0001 | 0.149 | 0.348 |

$^{\#}$natural log
*Antwerp vs Decatur
**1994/95 vs 1997

Table 19. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of AST[#] Change Including PFOS and the Interaction with Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| Intercept | 3.080 | 0.198 | <.0001 | 2.689 | 3.471 |
| PFOS | 0.010 | 0.011 | .39 | -0.013 | 0.032 |
| Years Observation | -0.009 | 0.007 | .19 | -0.024 | 0.005 |
| PFOS x Years Obs | 0.0007 | 0.003 | .79 | -0.005 | 0.006 |
| Age | -0.008 | 0.004 | .05 | -0.016 | -0.00005 |
| BMI | 0.004 | 0.005 | .47 | -0.007 | 0.014 |
| Drinks/day | 0.030 | 0.018 | .11 | -0.007 | 0.066 |
| Cigarettes/day | -0.003 | 0.002 | .07 | -0.006 | 0.0002 |
| Location* | 0.102 | 0.053 | .06 | -0.206 | 0.003 |
| Entry Period** | 0.039 | 0.039 | .32 | -0.038 | 0.116 |
| Baseline Years Worked | 0.005 | 0.004 | .22 | -0.003 | 0.012 |
| Triglycerides# | 0.063 | 0.029 | .03 | 0.005 | 0.121 |

#natural log
*Antwerp vs Decatur
**1994/95 vs 1997

Table 20.  Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of AST[#] Change Including PFOA and the Interaction with
Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 3.053 | 0.199 | <.0001 | 2.661 | 3.445 |
| PFOA | 0.027 | 0.015 | .06 | - 0.002 | 0.056 |
| Years Observation | - 0.008 | 0.007 | .28 | - 0.022 | 0.006 |
| PFOA x Years Obs | - 0.002 | 0.003 | .41 | - 0.008 | 0.003 |
| Age | - 0.007 | 0.004 | .08 | - 0.015 | 0.0008 |
| BMI | 0.004 | 0.005 | .39 | - 0.006 | 0.015 |
| Drinks/day | 0.030 | 0.018 | .10 | - 0.006 | 0.066 |
| Cigarettes/day | - 0.003 | 0.002 | .07 | - 0.006 | 0.0002 |
| Location* | - 0.097 | 0.053 | .07 | - 0.201 | 0.008 |
| Entry Period** | 0.044 | 0.039 | .26 | - 0.032 | 0.120 |
| Baseline Years Worked | 0.004 | 0.004 | .27 | - 0.003 | 0.012 |
| Triglycerides[#] | 0.054 | 0.030 | .07 | - 0.004 | 0.113 |

[#]natural log
*Antwerp vs Decatur
**1994/95 vs 1997

Table 21. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of $AST^{\#}$ Change Including TOF and the Interaction with Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 3.058 | 0.198 | <.0001 | 2.666 | 3.449 |
| TOF | 0.018 | 0.011 | .12 | - 0.005 | 0.04 |
| Years Observation | - 0.009 | 0.008 | .24 | - 0.024 | 0.006 |
| TOF x Years Obs | - 0.006 | 0.002 | .79 | - 0.005 | 0.004 |
| Age | - 0.008 | 0.004 | .06 | - 0.016 | 0.0002 |
| BMI | 0.004 | 0.005 | .40 | - 0.006 | 0.015 |
| Drinks/day | 0.029 | 0.018 | .12 | - 0.007 | 0.065 |
| Cigarettes/day | - 0.003 | 0.002 | .07 | - 0.006 | 0.0002 |
| Location* | - 0.095 | 0.053 | .08 | - 0.199 | 0.010 |
| Entry Period** | 0.039 | 0.039 | .31 | - 0.037 | 0.115 |
| Baseline Years Worked | 0.005 | 0.004 | .24 | - 0.003 | 0.012 |
| Triglycerides# | 0.058 | 0.029 | .05 | 0.00003 | 0.116 |

\# natural log
*Antwerp vs Decatur
**1994/95 vs 1997

Table 22. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of ALT# Change Including PFOS and the Interaction with Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 2.501 | 0.273 | <.0001 | 1.961 | 3.041 |
| PFOS | 0.010 | 0.016 | .54 | -0.021 | 0.041 |
| Years Observation | -0.095 | 0.010 | <.0001 | -0.115 | -0.075 |
| PFOS x Years Obs | -0.00003 | 0.004 | .99 | -0.008 | 0.008 |
| Age | 0.0009 | 0.006 | .88 | -0.012 | 0.010 |
| BMI | 0.010 | 0.007 | .17 | -0.004 | 0.024 |
| Drinks/day | -0.012 | 0.025 | .63 | -0.062 | 0.038 |
| Cigarettes/day | -0.008 | 0.002 | .001 | -0.012 | -0.003 |
| Location* | -0.088 | 0.073 | .23 | -0.233 | 0.056 |
| Entry Period** | 0.329 | 0.054 | <.0001 | 0.222 | 0.436 |
| Baseline Years Worked | 0.001 | 0.005 | .84 | -0.010 | 0.012 |
| Triglycerides# | 0.159 | 0.040 | .0001 | 0.079 | 0.238 |

#natural log
*Antwerp vs Decatur
**1994/95 vs 1997

Table 23. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of ALT[#] Change Including PFOA and the Interaction with
Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 2.479 | 0.272 | <.0001 | 1.942 | 3.016 |
| PFOA | 0.015 | 0.020 | .46 | -0.025 | 0.054 |
| Years Observation | -0.107 | 0.010 | <.0001 | -0.126 | -0.087 |
| PFOA x Years Obs | 0.005 | 0.004 | .19 | -0.003 | 0.013 |
| Age | -0.0001 | 0.006 | .98 | -0.011 | 0.011 |
| BMI | 0.011 | 0.007 | .13 | -0.003 | 0.025 |
| Drinks/day | -0.009 | 0.025 | .72 | -0.058 | 0.040 |
| Cigarettes/day | -0.007 | 0.002 | .001 | -0.012 | -0.003 |
| Location* | -0.079 | 0.072 | .28 | -0.222 | 0.064 |
| Entry Period** | 0.330 | 0.053 | <.0001 | 0.225 | 0.434 |
| Baseline Years Worked | 0.0008 | 0.005 | .89 | -0.010 | 0.011 |
| Triglycerides[#] | 0.151 | 0.041 | .0003 | 0.071 | 0.231 |

[#]natural log
*Antwerp vs Decatur
**1994/95 vs 1997

Table 24. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of ALT[#] Change Including TOF and the Interaction with Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | 2.476 | 0.273 | <.0001 | 1.936 | 3.015 |
| TOF | 0.020 | 0.016 | .21 | -0.011 | 0.051 |
| Years Observation | -0.102 | 0.011 | <.0001 | -0.123 | -0.082 |
| TOF x Years Obs | 0.002 | 0.003 | .50 | -0.004 | 0.008 |
| Age | -0.0005 | 0.006 | .93 | -0.011 | 0.010 |
| BMI | 0.011 | 0.007 | .11 | -0.003 | 0.026 |
| Drinks/day | -0.013 | 0.025 | .62 | -0.062 | 0.037 |
| Cigarettes/day | -0.008 | 0.002 | .001 | -0.012 | -0.003 |
| Location* | -0.073 | 0.073 | .32 | -0.217 | 0.072 |
| Entry Period** | 0.325 | 0.053 | <.0001 | 0.220 | 0.430 |
| Baseline Years Worked | 0.0008 | 0.005 | .88 | -0.010 | 0.011 |
| Triglycerides* | 0.148 | 0.040 | .0003 | 0.069 | 0.228 |

#natural log
*Antwerp vs Decatur
**1994/95 vs 1997

000310

Table 25. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of Total Bilirubin* Change Including PFOS and the Interaction with
Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | - 0.334 | 0.241 | .17 | - 0.811 | 0.142 |
| PFOS | - 0.018 | 0.014 | .22 | - 0.046 | 0.011 |
| Years Observation | 0.033 | 0.009 | .0005 | 0.0148 | 0.052 |
| PFOS x Years Obs | - 0.002 | 0.004 | .94 | - 0.007 | 0.007 |
| Age | 0.011 | 0.005 | .02 | 0.001 | 0.020 |
| BMI | - 0.003 | 0.007 | .67 | - 0.016 | 0.010 |
| Drinks/day | 0.016 | 0.024 | .50 | - 0.030 | 0.062 |
| Cigarettes/day | - 0.008 | 0.002 | <.0001 | - 0.012 | - 0.004 |
| Location* | 0.315 | 0.064 | <.0001 | 0.189 | 0.441 |
| Entry Period** | - 0.114 | 0.047 | .02 | - 0.206 | - 0.022 |
| Baseline Years Worked | - 0.002 | 0.005 | .64 | - 0.011 | 0.007 |
| Triglycerides* | - 0.088 | 0.037 | .02 | - 0.161 | - 0.015 |

*natural log
*Antwerp vs Decatur
**1994/95 vs 1997

Table 26. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of Total Bilirubin# Change Including PFOA and the Interaction with Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | -0.315 | 0.242 | .19 | -0.793 | 0.162 |
| PFOA | -0.030 | 0.019 | .16 | 0.066 | 0.007 |
| Years Observation | 0.028 | 0.009 | .003 | 0.001 | 0.046 |
| PFOA x Years Obs | 0.005 | 0.004 | .18 | -0.002 | 0.013 |
| Age | 0.010 | 0.005 | .04 | 0.0007 | 0.020 |
| BMI | -0.003 | 0.007 | .61 | -0.016 | 0.010 |
| Drinks/day | 0.014 | 0.023 | .55 | -0.032 | 0.060 |
| Cigarettes/day | -0.008 | 0.002 | <.0001 | -0.013 | -0.004 |
| Location* | 0.318 | 0.064 | <.0001 | 0.193 | 0.444 |
| Entry Period** | -0.124 | 0.046 | .007 | -0.215 | -0.034 |
| Baseline Years Worked | -0.002 | 0.005 | .71 | -0.011 | 0.007 |
| Triglycerides# | -0.082 | 0.037 | .03 | -0.156 | -0.008 |

#natural log
*Antwerp vs Decatur
**1994/95 vs 1997

Table 27. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of Total Bilirubin[#] Change Including TOF and the Interaction with
Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| --- | --- | --- | --- | --- | --- |
| | | | | Lower | Upper |
| Intercept | - 0.318 | 0.242 | .19 | - 0.796 | 0.160 |
| TOF | - 0.020 | 0.014 | .16 | - 0.049 | 0.008 |
| Years Observation | 0.029 | 0.010 | .005 | 0.009 | 0.049 |
| TOF x Years Obs | 0.003 | 0.003 | .36 | - 0.003 | 0.009 |
| Age | 0.011 | 0.005 | .03 | 0.001 | 0.020 |
| BMI | - 0.003 | 0.007 | .65 | - 0.016 | 0.010 |
| Drinks/day | 0.016 | 0.023 | .51 | - 0.031 | 0.062 |
| Cigarettes/day | - 0.008 | 0.002 | < .0001 | - 0.012 | - 0.004 |
| Location* | 0.316 | 0.064 | < .0001 | 0.190 | 0.442 |
| Entry Period** | 0.120 | 0.046 | .01 | - 0.210 | - 0.029 |
| Baseline Years Worked | - 0.002 | 0.005 | .68 | - 0.011 | 0.007 |
| Triglycerides[#] | - 0.085 | 0.037 | .02 | - 0.158 | - 0.012 |

[#] natural log
* Antwerp vs Decatur
** 1994/95 vs 1997

Table 28.  Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of Direct Bilirubin# Change Including PFOS and the Interaction with
Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits Lower | Upper |
|---|---|---|---|---|---|
| Intercept | - 1.756 | 0.204 | <.0001 | - 2.160 | - 1.355 |
| PFOS | - 0.013 | 0.013 | .29 | - 0.039 | 0.012 |
| Years Observation | - 0.097 | 0.009 | <.0001 | - 0.116 | -0.079 |
| PFOS x Years Obs | - 0.006 | 0.004 | .18 | - 0.014 | 0.003 |
| Age | 0.007 | 0.004 | .06 | - 0.0003 | 0.015 |
| BMI | - 0.003 | 0.006 | .58 | - 0.015 | 0.008 |
| Drinks/day | 0.018 | 0.020 | .37 | - 0.022 | 0.058 |
| Cigarettes/day | - 0.0005 | 0.002 | .79 | - 0.004 | 0.003 |
| Location* | 0.076 | 0.053 | .15 | - 0.028 | 0.180 |
| Entry Period** | 0.353 | 0.038 | <.0001 | 0.277 | 0.428 |
| Baseline Years Worked | - 0.001 | 0.004 | .74 | - 0.009 | 0.006 |
| Triglycerides# | - 0.090 | 0.033 | .006 | - 0.155 | -0.026 |

#natural log
*Antwerp vs Decatur
**1994/95 vs 1997

Table 29. Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits from Testing Potential Determinants of Direct Bilirubin[#] Change Including PFOA and the Interaction with Number of Years of Observation of Antwerp and Decatur Male Employees

|  | Coefficient | SE | p-value | 95% Confidence Limits | |
|---|---|---|---|---|---|
|  |  |  |  | Lower | Upper |
| Intercept | - 1.753 | 0.207 | <.0001 | - 2.161 | - 1.345 |
| PFOA | - 0.012 | 0.017 | .47 | - 0.045 | 0.021 |
| Years Observation | - 0.095 | 0.009 | <.0001 | - 0.113 | - 0.077 |
| PFOA x Years Obs | - 0.004 | 0.004 | .27 | - 0.012 | 0.003 |
| Age | 0.006 | 0.004 | .11 | - 0.001 | 0.014 |
| BMI | - 0.003 | 0.006 | .66 | - 0.014 | 0.009 |
| Drinks/day | 0.014 | 0.020 | .50 | - 0.026 | 0.053 |
| Cigarettes/day | - 0.0005 | 0.002 | .80 | - 0.004 | 0.003 |
| Location* | 0.083 | 0.053 | .12 | - 0.022 | 0.188 |
| Entry Period** | 0.345 | 0.038 | <.0001 | 0.271 | 0.420 |
| Baseline Years Worked | - 0.0008 | 0.004 | .83 | - 0.008 | 0.007 |
| Triglycerides[#] | - 0.089 | 0.033 | .009 | - 0.155 | - 0.023 |

[#]natural log
*Antwerp vs Decatur
**1994/95 vs 1997

Table 30.  Mixed Model Coefficient Estimates, Standard Errors (SE), P-Values and 95% Confidence Limits
from Testing Potential Determinants of Direct Bilirubin# Change Including TOF and the Interaction with
Number of Years of Observation of Antwerp and Decatur Male Employees

| | Coefficient | SE | p-value | 95% Confidence Limits | |
| | | | | Lower | Upper |
|---|---|---|---|---|---|
| Intercept | - 1.748 | 0.205 | <.0001 | - 2.154 | - 1.343 |
| TOF | - 0.013 | 0.013 | .33 | - 0.038 | 0.013 |
| Years Observation | - 0.093 | 0.010 | <.0001 | - 0.113 | - 0.073 |
| TOF x Years Obs | - 0.004 | 0.003 | .21 | - 0.011 | 0.002 |
| Age | 0.007 | 0.004 | .08 | - 0.0008 | 0.014 |
| BMI | - 0.003 | 0.006 | .57 | - 0.015 | 0.008 |
| Drinks/day | 0.017 | 0.020 | .39 | - 0.022 | 0.057 |
| Cigarettes/day | - 0.0004 | 0.002 | .84 | - 0.004 | 0.003 |
| Location* | 0.074 | 0.053 | .16 | - 0.031 | 0.179 |
| Entry Period** | 0.349 | 0.038 | <.0001 | 0.274 | 0.424 |
| Baseline Years Worked | - 0.001 | 0.004 | .77 | - 0.008 | 0.006 |
| Triglycerides# | - 0.087 | 0.033 | .009 | - 0.152 | - 0.022 |

#natural log
*Antwerp vs Decatur
**1994/95 vs 1997

000316

# Benchmark Doses for Tumors in Sprague Dawley Rats fed N-Ethyl Perfluorooctanesulfonamido Ethanol (N-EtFOSE)

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January 31, 2002

## Introduction

The carcinogen risk assessment guidelines proposed by the U.S. Environmental Protection Agency (1999) recommend the use of a benchmark dose (BMD) approach for low dose cancer risk assessment. Unless stipulated otherwise, the BMD is the dose at which the excess lifetime tumor incidence is 10%, denoted by $BMD_{10}$. A value of 10% was selected as this is about the lowest incidence that can be estimated with adequate precision from typical chronic bioassays in rodents. Further, a lower 95% confidence limit is calculated for the benchmark dose ($BMDL_{10}$) to account for the experimental variation of the bioassay. The $BMDL_{10}$ is then used as a point-of-departure for low dose cancer risk assessment. When a nonlinear dose response curve is expected in the low dose range, a margin of exposure between the $BMDL_{10}$ and anticipated human exposure levels is considered. Otherwise, linear extrapolation from the $BMDL_{10}$ to zero is used for low dose cancer risk estimation. In either case, the $BMDL_{10}$ serves as the point-of-departure.

## Bioassay Data

The data used for calculation of the $BMDL_{10}$ were collected in the 104-Week Dietary Carcinogenicity Study with Narrow Range (98.1%) N-Ethyl Perfluorooctanesulfonamido Ethanol in Rats. The BMDL is calculated for thyroid follicar cell adenomas and carcinomas combined in males and for hepatocellular adenomas and carcinomas combined for females. All tumors were adenomas except for one carcinoma in the 30 mg/kg group in males and one carcinoma in the 100 mg/kg females.

In order to calculate lifetime incidence rates for each dose group, it is necessary to calculate the number of animals at risk. Clearly, animals that were removed from the study for interim sacrifices or that died before the terminal sacrifice were not at risk for a lifetime. The Poly-3 approach developed by the National Toxicology Program (Bailer and Portier, 1988) is used here to calculate the effective number of animals at risk. Obviously, an animal that survives for the lifetime of the study until the terminal sacrifice counts as a whole lifetime exposure. Also, any animal that is removed from the study with a tumor of interest (thyroid follicular cell in males or hepatocellular in females) prior to the terminal sacrifice lived long enough to develop the tumor is counted as a lifetime exposure. All other animals are given a weight of $(t/T)^3$, where t is the week that an animal was removed from the study without the tumor of interest and terminal sacrifices began at

week T=105. Relatively little weight is given to an animal removed early in a study. For example, the animals removed at an interim sacrifice halfway through the study at 53 weeks receive a weight of $(53/105)^3 = 0.13$ of a lifetime, whereas an animal that died on week 96 receives a weight of $(96^3/105) = 0.76$ of a lifetime. The weights are summed for each dose group to obtain the effective number of animals at risk for each group.

The number of male rats with thyroid follicular cell adenomas or carcinomas combined, effective number of animals at risk, and average serum levels of PFOS at 14 weeks for each dose group are displayed in Table 1.

Table 1. Results from the 104-week carcinogenicity study in male SD rats fed N-EtFOSE.

| Group | Dose (ppm) | Serum PFOS at 14 weeks (ug/ml) | Number of rats with thyroid tumors[a] | Effective number of rats at risk |
|---|---|---|---|---|
| 1 | 0 | 0.078 | 0 | 34 |
| 2 | 3 | 6.14 | 3 | 35 |
| 3 | 30 | 59.1 | 2 | 36 |
| 4 | 100 | 192 | 6 | 37 |
| 8 | 0 | 0.039 | 1 | 34 |
| 9 | 1 | 2.19 | 2 | 37 |

[a] Thyroid follicular cell adenomas except one carcinoma in Group 3.

The number of female rats with hepatocellular adenomas or carcinomas combined, effective number of animals at risk, and the average serum levels of PFOS at 14 weeks are shown in Table 2.

Table 2.  Results from the 104-week carcinogenicity study in female SD rats fed N-EtFOSE.

| Group | Dose (ppm) | Serum PFOS at 14 weeks (ug/ml) | Number of rats with liver tumors[a] | Effective number of rats at risk |
|-------|-----------|-------------------------------|-------------------------------------|----------------------------------|
| 1 | 0 | 0.196 | 0 | 32 |
| 2 | 3 | 12.2 | 1 | 32 |
| 3 | 30 | 104 | 3 | 33 |
| 4 | 100 | 268 | 7 | 38 |
| 8 | 0 | 0.126 | 2 | 33 |
| 9 | 1 | 3.26 | 1 | 36 |

[a] Hepatocellular adenomas except one carcinoma in Group 4.

**Benchmark Dose Calculations**

The numbers of animals with hepatocellular adenoma/carcinoma and the effective number of animals at risk were entered into the U.S. Environmental Protection Agency benchmark dose software program (BMDS).  Estimates of the benchmark dose were obtained using the multistage model

$$P = 1 - \exp[-( q_0 + q_1 d + q_2 d^2 + q_3 d^3 + q_4 d^4 )]$$

where P represents the proportion of animals with tumors, d is the dietary dose or serum level, and the q's are estimated from the experimental dose response data. Goodness-of-fit p-values for the multistage model are above 0.1 indicating an adequate fit of the model.  Small p-values would indicate a statistically significant deviance from the multistage model.  The goodness-of-fit p-values, $BMD_{10}$, and $BMDL_{10}$ in terms of dietary concentration of N-EtFOSE and 14-week serum levels of PFOS for males and females are displayed in Table 3.

Table 3. Goodness-of-fit p-values for the multistage model, $BMD_{10}$, and $BMDL_{10}$ values obtained using the US EPA benchmark dose software program (BMDS).

| Sex | p-value | $BMD_{10}$ | $BMDL_{10}$ |
|---|---|---|---|
| Dietary Concentration | | | |
| Male | 0.23 | 89 ppm | 40 ppm |
| Female | 0.99 | 58 ppm | 32 ppm |
| 14-Week Serum Level | | | |
| Male | 0.23 | 171 ug/ml | 77 ug/ml |
| Female | 0.98 | 166 ug/ml | 91 ug/ml |

**References**

Bailer, A.J. and Portier, C.J. Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples. *Biometrics* 44:417-431 (1988).

U.S. Environmental Protection Agency. *Guidelines for Carcinogen Risk Assessment.* NCEA-F-0644, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC. July, 1999.

# Benchmark Doses for Liver Tumors in Sprague Dawley Rats fed Perfluorooctane Sulfonic Acid Potassium Salt (PFOS)

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January 24, 2002

## Introduction

The carcinogen risk assessment guidelines proposed by the U.S. Environmental Protection Agency (1999) recommend the use of a benchmark dose (BMD) approach for low dose cancer risk assessment. Unless stipulated otherwise, the BMD is the dose at which the excess lifetime tumor incidence is 10%, denoted by $BMD_{10}$. A value of 10% was selected as this is about the lowest incidence that can be estimated with adequate precision from typical chronic bioassays in rodents. Further, a lower 95% confidence limit is calculated for the benchmark dose ($BMDL_{10}$) to account for the experimental variation of the bioassay. The $BMDL_{10}$ is then used as a point-of-departure for low dose cancer risk assessment. When a nonlinear dose response curve is expected in the low dose range, a margin of exposure between the $BMDL_{10}$ and anticipated human exposure levels is considered. Otherwise, linear extrapolation from the $BMDL_{10}$ to zero is used for low dose cancer risk estimation. In either case, the $BMDL_{10}$ serves as the point-of-departure.

## Bioassay Data

The data used for calculation of the $BMDL_{10}$ were collected in the 104-Week Dietary Chronic Toxicity and Carcinogenicity Study with Perfluorooctane Sulfonic Acid Potassium Salt (PFOS; T-6295) in Rats. The BMDL is calculated for hepatocellular adenomas and carcinomas combined for males and females. All tumors were adenomas except for one carcinoma in the high dose females.

In order to calculate lifetime incidence rates for each dose group, it is necessary to calculate the number of animals at risk. Clearly, animals that were removed from the study for interim sacrifices or that died before the terminal sacrifice were not at risk for a lifetime. The Poly-3 approach developed by the National Toxicology Program (Bailer and Portier, 1988) is used here to calculate the effective number of animals at risk. Obviously, an animal that survives for the lifetime of the study until the terminal sacrifice counts as a whole lifetime exposure. Also, any animal that is removed from the study with a hepatocellular adenoma/carcinoma prior to the terminal sacrifice lived long enough to develop the tumor is counted as a lifetime exposure. All other animals are given a weight of $(t/T)^3$, where t is the week that an animal was removed from the study without a hepatocellular adenoma/carcinoma and terminal sacrifices began at week T=105.. Relatively little weight is given to an animal removed early in a study. For example, the animals removed at an interim sacrifice halfway through the study

at 53 weeks receive a weight of $(53/105)^3 = 0.13$ of a lifetime, whereas an animal that died on week 96 receives a weight of $(96^3/105) = 0.76$ of a lifetime. The weights are summed for each dose group to obtain the effective number of animals at risk for each group.

The number of animals with hepatocellular adenoma/carcinoma, effective number of animals at risk, and average serum levels of PFOS at 14 weeks for each dose group are displayed in Table 1.

Table 1. Results from the 104-week carcinogenicity study in SD rats fed PFOS.

| Dose (ppm) | 14-wk Serum (ug/ml) | Number of animals with liver tumors[a] | Effective number of animals |
|---|---|---|---|
| | | Males | |
| 0 | 0.05 | 0 | 33 |
| 0.5 | 4.04 | 3 | 32 |
| 2.0 | 17.1 | 3 | 37 |
| 5.0 | 43.9 | 1 | 38 |
| 20.0 | 148 | 7 | 38 |
| | | Females | |
| 0 | 2.67 | 0 | 39 |
| 0.5 | 6.96 | 1 | 35 |
| 2.0 | 27.3 | 1 | 29 |
| 5.0 | 64.4 | 1 | 37 |
| 20.0 | 223 | 6 | 41 |

[a] Hepatocellular adenomas except one hepatocellular carcinoma in the high dose females.

As noted before, the effective numbers of animals at risk reflect the lower survival in the controls and low dose males and the females fed 2 ppm and the higher survival in the high dose females.

**Benchmark Dose Calculations**

The numbers of animals with hepatocellular adenoma/carcinoma and the effective number of animals at risk were entered into the U.S. Environmental Protection Agency benchmark dose software program (BMDS). Estimates of the benchmark dose were obtained using the multistage model

$$P = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + q_3 d^3 + q_4 d^4)]$$

where P represents the proportion of animals with tumors, d is the dietary dose or serum level, and the q's are estimated from the experimental dose response data. Goodness-of-fit p-values for the multistage model are above 0.1 indicating an adequate fit of the model. Small p-values would indicate a statistically significant deviance from the multistage model. The goodness-of-fit p-values, $BMD_{10}$, and $BMDL_{10}$ in terms of dietary concentration and 14-week serum levels of PFOS for males and females are displayed in Table 2.

Table 2. Goodness-of-fit p-values for the multistage model, $BMD_{10}$, and $BMDL_{10}$ values obtained using the US EPA benchmark dose software program (BMDS).

| Sex | p-value | $BMD_{10}$ | $BMDL_{10}$ |
|---|---|---|---|
| *Dietary Concentration* | | | |
| Male | 0.24 | 18.2 ppm | 7.9 ppm |
| Female | 0.54 | 16.7 ppm | 8.0 ppm |
| *14-Week Serum Level* | | | |
| Male | 0.23 | 135 ug/ml | 62 ug/ml |
| Female | 0.54 | 193 ug/ml | 92 ug/ml |

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## References

Bailer, A.J. and Portier, C.J. Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples. *Biometrics* 44:417-431 (1988).

U.S. Environmental Protection Agency. *Guidelines for Carcinogen Risk Assessment.* NCEA-F-0644, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC. July, 1999.